STUDIES

FROM THE

LABORATORIES

OF THE

PHILADELPHIA GENERAL HOSPITAL

DEPARTMENT OF HEALTH, CITY OF PHILADELPHIA

C. LINCOLN FURBUSH, M.D., DIRECTOR OF HEALTH
E. B. KRUMBHAAR M.D., DIRECTOR OF LABORATORIES

COLLECTED REPRINTS

VOLUME I

PHILADELPHIA
1920–1923

LIST OF PERSONNEL.

Edward B. Krumbhaar, Director of Laboratories 1920

Pathology.

Allen J. Smith, Visiting Pathologist 1903
Joseph McFarland, Visiting Pathologist 1900
W. M. L. Coplin, Visiting Pathologist 1896–1922
Balduin Lucké, Assistant Visiting Pathologist 1914
Morton McCutcheon, Assistant Visiting Pathologist 1920
John Eiman, Assistant Visiting Pathologist 1919
Eugene A. Case, Assistant Visiting Pathologist 1919
F. Hartman, Assistant Visiting Pathologist 1921
B. L. Crawford, Assistant Visiting Pathologist 1920
E. Weiss, Assistant Visiting Pathologist 1920–1922
F. Konzelman, Assistant Visiting Pathologist 1922
S. S. Schochet, Assistant Visiting Pathologist 1922

Histology.

W. P. Belk, Histologist 1920
H. E. Radasch, Assistant Histologist 1920–1921
J. H. Smith, Assistant Histologist 1921

Anatomy.

E. T. Crossan, Anatomist 1920
H. McH. Miller, Anatomist 1920–1921
A. G. Kershner, Anatomist 1920–1922
W. J. Freeman, Anatomist 1920–1921
D. Hinton, Anatomist 1921–1922
J. P. Scott, Anatomist 1921
W. J. Gilmour, Anatomist 1922

J. P. Stinson, Resident Pathologist 1923–1923
R. S. McGinnis, Resident Pathologist 1923

Neuropathology.

N. W. Winkelman, Neuropathologist 1920
Clarence Patten, Assistant Neuropathologist 1920–1922
Walter J. Freeman, Assistant Neuropathologist 1922

Clinical Pathology.

Arthur D. Waltz, Clinical Pathologist 1920–1923
Carlos D. Pons, Clinical Pathologist 1923

Bacteriology.

James C. Small, Bacteriologist	1920
L. Julianelle, First Assistant Bacteriologist	1920
Mrs. L. Evans, Second Assistant Bacteriologist	1920
Mrs. E. White, Serologist	1920–1921
Miss C. Stam, Serologist	1921

Biochemistry.

G. H. Meeker, Consulting Biochemist	1919
W. G. Karr, Biochemist	1921
Miss C. Buckwalter, Assistant Biochemist	1920–1921
A. J. Quick, Assistant Biochemist	1921–1922
B. L. Oser, Assistant Biochemist	1922
W. H. Stoner, Second Assistant Biochemist	1920

J. Edwin Sweet, Consulting Surgeon	1922
Erwin F. Faber, Consulting Artist	1922
Howard Gosner, Curator	1920

William Hewson, Electrocardiographer	1920–1921
Thomas MacMillan, Electrocardiographer	1921

Radiological Department.

J. L. Weatherwax, Physicist	1921

Moses Behrend, Volunteer in Research	1922
Alfred Chanutin, Volunteer in Research	1921–1921
McKean Downs, Volunteer in Research	1921–1921
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PREFACE.

WITH the installation of the new laboratories of the Philadelphia General Hospital in 1920, the hope was expressed on many sides that it would become possible to make better use of the vast available material for productive research. This volume is the first response, and is made possible largely through the favorable attitude and assistance of the Director of Public Health and Dr. J. C. Doane, the Medical Director of the Hospital.

The organization and functions of the staff has already been described in one of the accompanying reprints. Although all the laboratories have been more or less productive, for various reasons they are represented by work in this volume in different degrees. The Biochemical Laboratory, for instance, not only took necessarily longer time to get properly installed, but also has several productive lines of work nearing completion or actually in press, the reprints of which have not been received.

It is greatly to be regretted that we were unable to secure the address made by Dr. William H. Welch at the opening of the new laboratories on the importance of the study of gross pathology. Arrangements were not made to have it taken by a stenographer, and as far as I can learn, it has never been committed to writing. As our policy has been to offer our facilities, as far as possible, to serious volunteers or colleagues in our own and neighboring institutions, I have not hesitated to include in this volume the result of their work, in which the laboratory studies played the most important part. In a few cases, the work has been done conjointly here and in other laboratories.

By placing this volume in the leading medical libraries and institutions of this and other countries, it is hoped not only that the results of our work will be somewhat more available to other workers in similar fields, but also that it will serve as a rough index of the productive capacity of the staff and a stimulus to further effort. With the great amount of routine work demanded by a large general hospital, which must, of course, be first properly cared for, it is not feasible to devote to special studies the prolonged and concentrated attention that is possible in a purely research institute. While, therefore, the list of articles may not seem large for a staff of our size, working for three years, we do not feel it altogether

discreditable, especially as many of the staff are working on part time. The character of the reports is also necessarily influenced by similar considerations, but, of course, every effort has been made to keep their quality at the highest possible level.

It is hoped that further volumes will appear from time to time, as sufficient material accumulates, and that exchanges may be made with similar publications throughout the world.

E. B. KRUMBHAAR,
Director of Laboratories.

THE EARLY HISTORY OF ANATOMY IN THE UNITED STATES

BY EDWARD B. KRUMBHAAR, PH.D., M.D.

Associate Professor of Applied Pathology, Graduate School of Medicine
University of Pennsylvania

FROM THE LABORATORIES OF THE PHILADELPHIA GENERAL HOSPITAL

IN as young a country as the United States, it is a comparatively easy matter to trace the growth of a science from its earliest beginning, and medicine is no exception to this rule. Thus we know the name of the first physician in the first permanent settlement in this country;[1] the doctor who accompanied the Pilgrims on the Mayflower in 1620;[2] the first Zieckentroosters or visitors of the sick in the Dutch colony of New York;[3] the three Welsh physicians who in 1682 came with William Penn in the Welcome to found Philadelphia and his colony of Pennsylvania;[4] and the author of the first medical work published in the United States.[5] The health of the struggling young communities was necessarily cared for at first by the more educated leaders, by midwives, by visiting ship's surgeons and by the few medical practitioners that had come from the mother country as colonists. But from the earliest times the need for occasional postmortem examinations and for learning the structure of the body from actual dissections ("Making an Anatomy"—in the quaint old term), rather than from book learning or didactic lectures, was well recognized. The difficulty of procuring anatomical material, which then existed throughout the civilized world, was most aggravated in the young, healthy and sparsely settled country; thus Eliot, the Apostle to the Indians, as early as 1647, expresses in a letter to Mr. Thomas Shepard, the Cambridge minister;[6] his desire that "our young Students in Physick may bee trained up better then yet they bee, who have only theoreticall knowledge, and are forced to fall to practice before ever they saw an Anatomy made, or duely trained up in making experiments, for we never had but one Anatomy in the Country, which Mr. Giles Firman (Firmin) (now in England) did make and read upon very well." In passing, it might be noted that Mr. Firmin found the outlook for the practice of physics in the new country so discouraging that he returned to England to take up the more lucrative study of divinity! The apostle's desire seems to have carried weight, as we find the following resolution passed within a month by the General Court of Massachusetts: "We conceive it very necessary yᵗ such as studies physick or chirurgery may have liberty to reade anotomy (sic) and to anotomize once in foure yeares some malefactor in case there be such as the Courte shall alow of."[7] In the same letter to Shepard, Eliot says, "I have shown them (i. e. the Indians) the anatomy of man's body," but Hartwell[8] thinks that Eliot probably never performed any dissections himself. The need for first-hand knowledge must have indeed been great—quackery was already rife, and the education of the practitioners often woefully lacking. Thus, in Judge Samuel Sewell's diary of September 22, 1676:[9] "Spent the day from nine in the morning with Mr. (Dr.) Brakenbury, Mr. Thomson, Butter, Hooper, Cragg, Pemberton, dissecting the middle-most of the Indians executed the day before. X., who taking the heart in hand, affirmed it to be the stomach." Packard[10] gives the record of six different autopsies reported in New England between the years 1674 and 1678, and Hartwell quotes from a Maryland Order of Council[11] what may well be the earliest autopsy performed in this country by legal direction. In 1691, the celebrated autopsy on Governor Slaughter of New York was made, which for a long time was erroneously considered to be the first re-

corded autopsy in this country. Governor Slaughter having incurred several severe enmities following the execution of a rioter, it was suspected that his sudden death might be due to poisoning. Dr. Johannes Kerfbyle,[12] assisted by five physicians, was therefore ordered by the Council to examine the body and reported that he "died of a defect in his blood and lungs

PORTRAIT OF THOMAS CADWALADER (1708–1779) IN POSSESSION OF THE PENNSYLVANIA HOSPITAL. THE ORIGINAL, BY CHARLES WILSON PEALE IN 1770, IS OWNED BY JOHN CADWALADER OF PHILADELPHIA.

occasioned by some glutinous tough humor in the blood, which stopped the passage thereof and occasioned its settling in the lungs." This, Walsh,[13] who gives an excellent description of the event, has ingeniously suggested to be the seventeenth century manner of describing a pulmonary embolism. From such accounts we may infer that in several of the American colonies at least, a post-mortem examination to determine the cause of death was not an uncommon occurrence in the seventeenth century. Of much later date (1750) was the well-known injection and dissection, by Drs. Thomas Bard and Peter Middleton of New York, of the body of Hermannus Carroll, an executed criminal,

"for the instruction of the young men then engaged in the study of medicine." Walsh states that they had offered a private course in anatomy before this date, but I do not know on what authority this statement is based.

Laudable and necessary as such efforts were, however, their benefits were mostly individual and evanescent, and it is to a different source that we must turn for the work that may be said to have initiated the scientific study of anatomy in the American colonies. The credit for this achievement may fairly be given to Dr. Thomas Cadwalader, one of the most notable Philadelphia physicians of the eighteenth century.

Thomas Cadwalader[14] (1707/8–1779) was the son of John Cadwalader, who emigrated from Wales in 1689, and Martha the daughter of Dr. Edward Jones. Having studied in the Friends "Publick" School (now the Penn Charter School), he was apprenticed at the mature age of eighteen for two years to his uncle, Dr. Evan Jones. He is thus doubly directly connected with the founding of the city, through two great-grandfathers: John Jones, who came over with Penn in 1699 and Dr. Thomas Wynne, one of the original settlers, the father-in-law of his grandfather, Edward Jones. To complete his medical education, he was sent to the University of Rheims and to England, where he studied under the celebrated William Cheselden, of whom Pope wrote, "I'll do what Mead and Cheselden advise, to keep these limbs and to preserve these eyes." Here presumably he learned the art of dissection, which was soon to stand him in such good stead. Shortly after his return from Europe (probably in 1730), he was known to be "so proficient in dissection, at that time rare in Europe and unknown in America, that students and physicians alike urged him to give a public course of lectures on the cadaver." Caspar Wistar[15] says: "According to correct information I find that on his return to Philadelphia he made dissections and demonstrations for the instruction of the elder Dr. Shippen and some others, who had not

been abroad." These demonstrations were given in a building on the back part of a lot on Second Street above Walnut, where later stood the old Bank of Philadelphia.[16] In Caspar Wistar's words, "this probably was the first business of the kind ever done in Pennsylvania." The impression that this event made in the mind of the elder Shippen was undoubtedly an important factor in sending his son to England for his medical education, which, as we shall later see, was the direct cause of the first scholastic teaching of anatomy in the American colonies.

Though nothing more is known of Cadwalader's anatomical dissections, he is known to have utilized his skill in this art throughout his career in the performance of autopsies. Thus, in his celebrated work on lead poisoning,[17] there are numerous notes of post-mortem observations and the "extraordinary case in physics" is a clinico-pathological report of a peculiar bone

A Page of Thomas Cadwalader's Manuscript of "An Essay on the West-India Dry-Gripes."

disease in a cured diabetic, written much in the modern style. It is not necessary or appropriate in this place to enumerate the various distinctions and honors that came to him in his long career through an event-

ful period of our history; nor to attempt to describe his personal charm, as exemplified in the well-known story of the demented Lieut. Bruluman in search of other game than that with which the Commons (now

A N

E S S A Y

On the *WEST-INDIA*

D R Y-G R I P E S;

W I T H T H E

Method of Preventing and Curing

T H A T

CRUEL DISTEMPER.

To which is added,

An Extraordinary *C A S E* in *Physick.*

PHILADELPHIA:

Printed and fold by B. F R A N K L I N. M.DCC.XLV.

Title Page of Cadwalader's "Essay on the West-India Dry-Gripes." The Copy in the Library of the College of Physicians is Unique in Having Two Prefaces.

City Hall Plaza) then abounded. One anecdote, recently told me by a descendant, I may be permitted to relate, as it has never to my knowledge appeared in print and throws an interesting light both on the man and his times. It seems that for some little time travelers along the Blockley (now Montgomery) Pike had been bothered by ghosts in the old Merion (Quaker) meeting churchyard (founded in 1683). Dr. Cadwalader therefore decided to investigate the

problem by spending the night on the premises, which were some six or eight miles from town. When the white apparition of the ghost appeared the worthy doctor gave chase around the graveyard and finally caught him, when he turned out to be a harmless lunatic at large.

Cadwalader's achievements in dissection and in morbid anatomy were the more noteworthy on account of the low level on which medicine stood in the colonies in the first half of the eighteenth century. Quacks were said to "abound like the locusts in Egypt" and complaints about charlatanism are only too numerous in the writings of the time. It is to be feared that the scurrilous words of Douglass,[18] a notable Scotch physician, who settled in Boston in 1718, have more than a modicum of truth:

> In our plantations, a practitioner, bold, rash, impudent, a lyar, basely born and uneducated, has much the advantage of an honest, cautious, modest gentleman. In general, the physical practice in our Colonies is so perniciously bad, that excepting in surgery and some acute cases, it is better to let nature take her course than to trust to the honesty and sagacity of the practitioner; our American practitioners are so rash and officious that the saying of the Apocrypha may, with propriety, be applied to them; "He that sinneth before his maker, let him fall into the hands of the physician." Frequently there is more danger from the physician than from the distemper.

In the latter half of the century, however, things medical were taking a distinct turn for the better. Not only did the growing wealth and strength of the colonies permit an ever-increasing number of ambitious students to visit the schools of Vienna, London and Edinburgh, in order to secure a scientific foundation for their medical studies, but also by the French and Indian wars many medical men of superior education were brought to the colonies. In the words of Dr. Nicholas Romaine:[19]

> The war which effected the conquest of Canada, was, perhaps, the first circumstance which materially improved the condition of medicine in this State (New York). The English army employed for that purpose, left Europe, accompanied by a highly respectable medical staff, most of whom landed in the city of New York, and continued some years in the neighboring territories, affording to many young Americans opportunities of attending the military hospitals, and receiving such professional instruction as gave them afterward consideration with the public. The physicians and surgeons of the Anglo-American army gained the confidence of the public, by their superior deportment and professional information. The military establishments in this State, after the Canadian war, required medical and surgical attendants, so that the people had the benefit of their advice. In this manner a new order of medical men was introduced into the Community.

Without the aid of medical schools, those who could not afford to go abroad, and many who could, acquired their training through the apprentice system, a method that was not without its advantages and which was at this time extensively followed in Europe as well. The young aspirant, after serving an appropriate time under indenture as the physician's technical—and often menial—assistant, thus acquired considerable skill in medical practice and in the necessary adjunct of pharmacy, but had little opportunity to study the underlying sciences. That these apprenticeships were no sinecure is shown by John Bard's service with the churlish Dr. Kearsley for seven years, beginning when he was fourteen. Benjamin Rush started with John Redman at fifteen and served for six years, and James Lloyd of Boston served with Clark for five years, beginning at the advanced age of seventeen. Though not especially connected with the teaching of Anatomy, a word at this point as to the flourishing condition of medicine in the Southern colonies of the eighteenth century seems desirable. In Charleston, especially, Lining, Moultrie, Chalmers and Garden formed a noteworthy group and the last named, with Mitchell of Virginia, constituted two of the fourteen American colonial Fellows of the Royal Society.

The earliest printed announcement of lectures on anatomy in this country was apparently that of Thomas Wood, Surgeon, who placed the following advertisement in the New York Weekly Postboy of January 27, 1752:[20]

Whereas Anatomy is allowed on all Hands, to be the Foundation both of PHYSICK and SURGERY, and consequently, without SOME knowledge of it, no person can be duly qualified to practice either: This is therefore to inform the Publick, That a COURSE of OSTEOLOGY and MYOLOGY, is intended to be begun, some Time in February next, in the City of New Brunswick, (for which Notice will be given in this Paper, as soon as a proper number have subscribed towards it). In which Course, all the human BONES will be separately examined, and their Connections and Dependencies on each other demonstrated; and all the MUSCLES of a human BODY dissected; the Origin, Insertion, and Use of each plainly shown. This Course is proposed to be finished in the Space of a Month.

THOMAS WOOD, Surgeon.

Such Gentlemen who are willing to attend this Course, are desired to subscribe their Names as soon as possible, with Mr. Richard Ayscough, Surgeon, at New York or said Thomas Wood, at New Brunswick, paying at the same Time, THREE POUNDS, Proc. and engaging to pay the said Sum of Three Pounds more, when the Course is half finished.

N. B. If proper Encouragement is given in this Course, he proposes soon after, to go thro' a Course of ANGIOLOGY and NEUROLOGY; and conclude, with performing all the OPERATIONS of SURGERY, on a dead body: The Use of which will appear to every Person, who considers the Necessity of having (at least) SEEN them performed, before he presumes to perform them himself on any living Fellow Creature.

Although this advertisement was subsequently repeated on several occasions in the same journal, I have been unable to find the notice mentioned, so do not know whether one or both courses were given, or if begun, how long they were continued. Wood's lectures, if given, antedated by two years the better known course of lectures on anatomy and comparative anatomy, given by William Hunter in Newport in 1754 to 1756. Hunter,[21] a Scotchman, born in 1720, was said to be a relative of his more famous namesake. Educated at Edinburgh under the elder Munro, and at Leyden, he came to Rhode Island in 1752 and quickly attained a position of prominence in the community. His medical library, at that time said to be the largest in New England, was mostly dispersed by accidents of the Revolution; but his manuscript lectures were still said to be in existence at a much later date, and his portrait still exists in the possession of a descendant of the same name, who is now employed in the United States Department of State.

While these sporadic efforts apparently complete the narrative of prescholastic instruction in anatomy in the American colonies, the record should not be considered discreditable in the light of the relatively immature state of that science in the home countries at that time.[22] Even on the Continent, where the study of Anatomy was most advanced, the Theatrum Anatomicum of Berlin was not founded till 1713 and the Vienna theatre in 1718, and the latter was practically without dissections till 1741. In Strasburg, Salzmann had daily dissections with three weekly demonstrations in 1708; but Haller, in Tubingen, was forced to study on dogs, and in Paris, on one occasion, fled for his life from a body-snatching episode. The celebrated Albinus averaged but one dissection a year at Leyden, Friedrich Hoffmann but twenty in twenty-four years at Halle; while in Prague there were but three dissections between 1692 and 1712. The earliest chairs of anatomy in England were all founded in the eighteenth century (Edinburgh, 1705; Cambridge, 1707; Glasgow, 1718; the Oxford lectureship, 1750*; Dublin, 1785).

* According to A. Chaplin (Contributions to Medical and Biological Research, Dedicated to Sir William Osler, 1919, i, 16), the Lee lectureship in Anatomy at Christ Church, Oxford, was founded in 1762.

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We now come to a more important and protracted effort in anatomical education, and of greater significance, as it led directly to the foundation of the first medical school in the American colonies. William Shippen, Sr., impressed with the advantages—denied to him—of a European education, and following the growing custom of the time, in 1758, sent his son, William, who had already studied physic with him for four years, to London to study anatomy with John Hunter and obstetrics with William Hunter, Smellie and McKenzie. In London young Shippen lived with John Hunter and worked in his home and in William Hunter's Theatre in Covent Garden, the Great Windmill Street School not being started until 1768. He became closely acquainted with the talented William Hewson, three years his junior, and the celebrated Quaker physician, John Fothergill, who had already evinced great constructive interest in the Quaker settlement of Philadelphia and especially in the newly founded (Quaker) Pennsylvania Hospital, the oldest general hospital in this country. Fothergill discussed with both Shippen and John Morgan, the desirability of establish-

JOHN FOTHERGILL
(1712–1780)

ing a medical school in the colonies, and probably had this in mind when, in 1762, he made his famous present to the Pennsylvania Hospital of the eighteen anatomical views and three cases of models.[23] The story of this gift and its influence on medical education has been so fully told elsewhere[24] that it need not be repeated here.

Shippen, after finishing his course under Cullen and Munro secundus and getting his degree at Edinburgh,[25] returned to Philadelphia in May 1762, and the same autumn began the successful course of anatomical lectures, which continued until interrupted by the Revolution in 1777. In the *Pennsylvania Gazette* of November 11, 1762, he issued the prospectus of his lectures, of which the introductory lecture was given at the State House on the 16th. Subsequent lectures were given in a building erected for the purpose in the rear of his father's residence on Fourth Street, and were doubtless largely based on the "curious Anatomical Casts and drawings, presented by the judicious and benevolent Doctor Fothergill," which the managers of the Pennsylvania Hospital generously loaned. Probably the skeleton presented by Deborah Morris to the Hospital in 1757, also played an important rôle; and in December the body of a negro who had committed suicide became available for dissection, and those of all criminals and suicides for some time thereafter.[26]

By the spring of 1765, Shippen's friend, John Morgan, was ready to return to America "to see whether, after fourteen years' devotion to medicine, I can get my living without turning apothecary or practicing surgery." But he had still weightier projects in hand, and before leaving Europe, he had already prepared a written Plan, which had the approval of the Hunters, Cullen, Fothergill and others, for the formation of a medical faculty in the flourishing young College of Philadelphia. This, with a letter of presentation to the Board of Trustees from Thomas Penn, proved so efficacious that on May 3, 1765, he was unanimously elected Professor of the Theory and Practice of Physic and the next September, in response to Dr. Shippen's "application" by letter, the latter was unanimously elected Professor of Anatomy and Surgery:
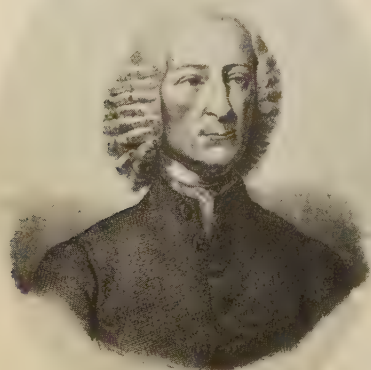
The instituting of medical schools in this country has been a favorite object of my attention for seven years past, and it is three years since I proposed the expediency and practicability of teaching medicine in all its branches in this city, in a public oration read at the State House, introductory to my first course of

14th, Shippen began the first course of lectures given in a medical school in this country. The joint announcement read as follows:

As the necessity for cultivating medical knowledge in America is allowed by all, it is

THE GYPSUM CASTS WHICH FOTHERGILL PRESENTED TO THE PENNSYLVANIA HOSPITAL.

Anatomy. I should have long since sought the patronage of the Trustees of this College, but waited to be joined by Dr. Morgan, to whom I first communicated my plan in England and who promised to unite with me in every scheme we might think necessary for the execution of so important a point.

I am pleased, however, to hear that you gentlemen, on being applied to by Dr. Morgan, have taken the plan under your protection and have appointed that gentleman Professor of Medicine.

A professorship of Anatomy and Surgery will be gratefully accepted by, gentlemen, your most obedient and humble servant.

WILLIAM SHIPPEN, JR.

Philadelphia, 17th September, 1765.

On September 26th, the prospectus of the newly founded Department appeared in the *Pennsylvania Gazette* and on November

with pleasure we inform the public that a Course of Lectures on two of the most important branches of that useful science, viz., Anatomy and Materia Medica, will be delivered this winter in Philadelphia. We have great reason, therefore, to hope that gentlemen of the Faculty will encourage the design by recommending it to their pupils, that pupils themselves will be glad of such an opportunity of improvement, and that the public will think it an object worthy their attention and patronage. In order to render these courses the more extensively useful, we intend to introduce into them as much of the Theory and Practice of Physic, of Pharmacy, Chemistry, and Surgery as can be conveniently admitted.

From all this, together with an attendance on the practice of the physicians and surgeons of the Pennsylvania Hospital, the students will be able to prosecute their studies with such advantage as will qualify them to practice

hereafter with more satisfaction to themselves and benefit to the community.

The particular advertisements inserted below specify the time when these lectures are to commence, and contain the various subjects to be treated of in each course, and the terms on which pupils are to be admitted.

WILLIAM SHIPPEN, JR., M. D.
Professor of Anatomy and Surgery in the College of Philadelphia

JOHN MORGAN M. D., F.R.S., Etc.
Professor of Medicine in the College of Philadelphia

Dr. Shippen's course of anatomical lectures will begin on Thursday, the 14th of November, 1765; it will consist of about sixty lectures, in which the situation, figure, and structure of all parts of the human body will be demonstrated on the fresh subject, their respective uses explained, and their diseases, with the indica-
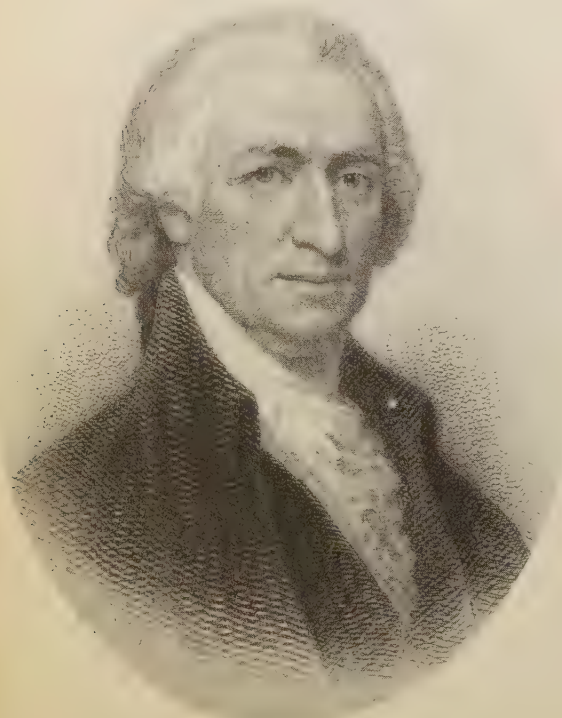
WILLIAM SHIPPEN, JR. (1736–1808), THE FIRST PROFESSOR OF ANATOMY IN BRITISH AMERICA.

tions and methods of cure, briefly treated of; all the necessary operations of Surgery will be performed, a course of bandages given; and the whole concluded with a few plain and general directions in the practice of midwifery. Each person to pay six pistoles.

Those who incline to attend the Pennsylvania Hospital and have the benefit of the curious anatomical plates and casts there, to pay six pistoles to that useful charity.

A course of lectures on the Materia Medica by John Morgan, M. D., etc. Price four pistoles.

This course will commence on Monday, the 18th day of November, and be given three times a week at the College, at three o'clock in the afternoon, till finished, which will last between three and four months.

To render these lectures as instructive as possible to students of physic, the Doctor proposes, in the course of them, to give some useful observations on Medicine in general, and the proper manner of conducting the study of physic. The authors to be read in the Materia Medica will be pointed out. The various substances made use of in medicine will be reduced under classes suited to the principal indications in the cure of diseases. Similar virtues in different plants, and their comparative powers will be treated of, and an inquiry made into the different methods which have been used in discovering the qualities of medicines, the virtues of the most efficacious will be particularly insisted upon; the manner of preparing and combining them will be shown by some instructive lessons upon pharmaceutic chemistry. This will open to students a general idea of both chemistry and pharmacy. To prepare them more effectually for understanding the art of prescribing with elegance and propriety, if time allows, it is proposed to include in this course some critical lectures upon the chief preparations contained in the Dispensatories of the Royal College at London and Edinburgh. The whole will be illustrated with many useful practical observations on Diseases, Diet and Medicines.

No person will be admitted without a ticket for the whole course. Those who propose to attend this course are desired to apply to the Doctor at least a week before the lectures begin. A dollar will be required of each student to matriculate, which will be applied to purchase books for a medical library in the College for the benefit of the medical students.

Thus was founded in the American Colonies their first medical faculty, which, through various vicissitudes, continued an uninterrupted course to its present proud position as the Medical Department of the

University of Pennsylvania. Since its foundation in 1765, there have been but seven occupants of this chair of anatomy: Shippen, Wistar, Dorsey (five months), Physick, Horner, Leidy and Piersol, truly a long

for the establishment of our first medical school, there would seem to be plenty for both of the chief actors. Shippen undoubtedly paved the way by his successful courses of anatomical lectures; as early as 1762,
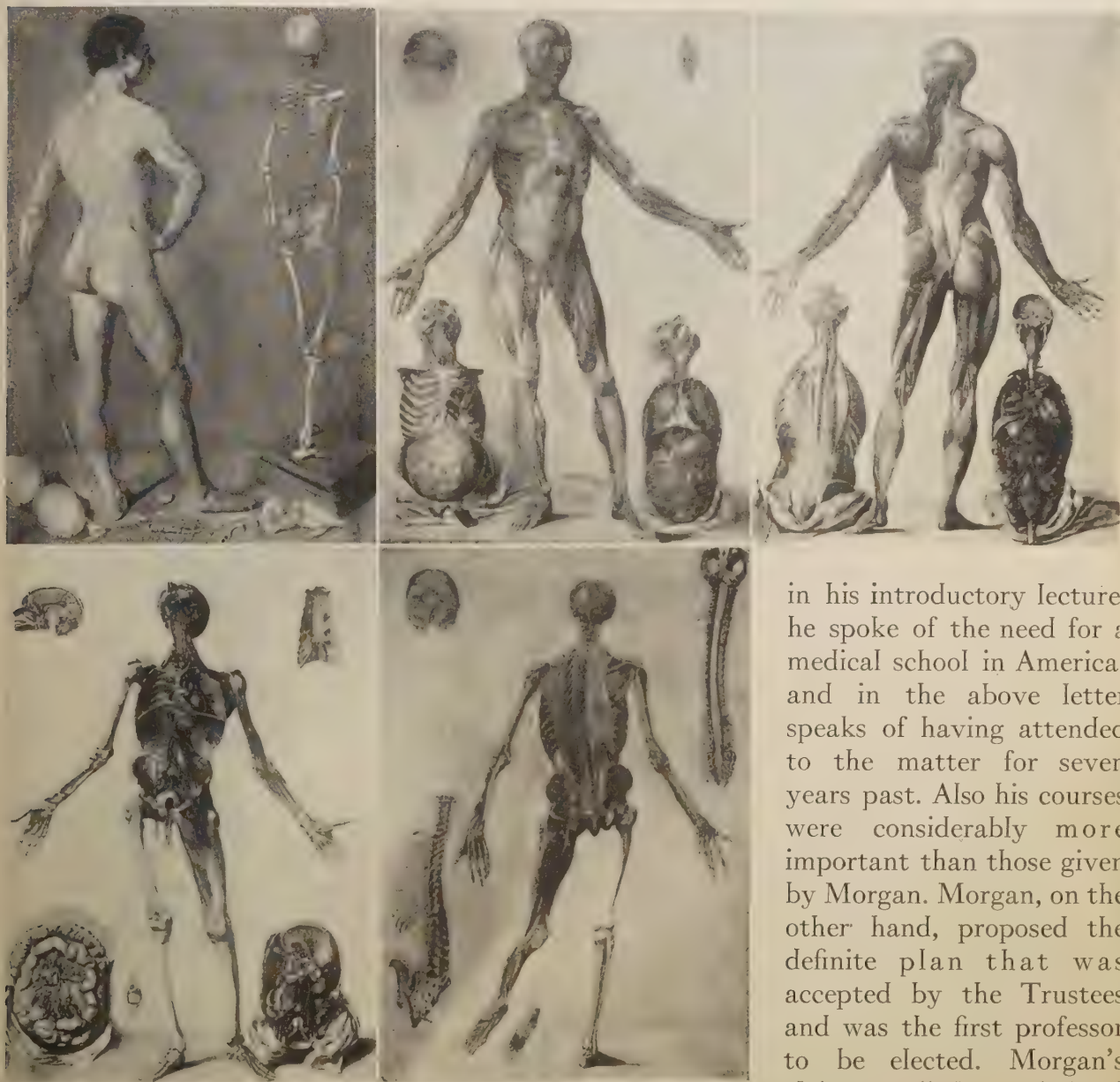
The Fothergill Crayons at the Pennsylvania Hospital on Which Shippen's Anatomical Lectures were Based.

in his introductory lecture, he spoke of the need for a medical school in America; and in the above letter speaks of having attended to the matter for seven years past. Also his courses were considerably more important than those given by Morgan. Morgan, on the other hand, proposed the definite plan that was accepted by the Trustees and was the first professor to be elected. Morgan's claim as "the original founder" was never to my

lived and big-minded group! The first degrees (Bachelors of Medicine) were given in 1767, and by statute, three years had to elapse before a thesis could be presented and a doctorate acquired. It is for this reason that the first doctor's degrees were given by the Medical School of King's College, N. Y., which only required a lapse of one year. In awarding the credit

knowledge disputed by the gentle, amiable Shippen. They worked together harmoniously on the new faculty, and though in the turmoil of Revolutionary, military medicine, trouble aplenty developed, why question this splendid achievement now?

One more item of the teaching of anatomy in Colonial Philadelphia may be included as a picturesque illustration of the times. In

1770, an English anatomist, Dr. Abraham Chovet, was forced by a slave insurrection in Jamaica to flee with his family and settled in Philadelphia. He brought with of the human body will be demonstrated, with their mechanisms and actions, together with the doctrines of life, health and the several effects resulting from the actions of the parts;

THE FOTHERGILL CRAYONS AT THE PENNSYLVANIA HOSPITAL ON WHICH SHIPPEN'S ANATOMICAL LECTURES WERE BASED.

him a series of wax anatomical models, which, with a collection of dried, injected and painted specimens, formed the basis for a series of anatomical lectures in the winter of 1774-75:

At the Anatomical Museum in Videl's alley, Second Street, on Wednesday, the Seventh of December at six in the evening Dr. Chovet will begin his course of Anatomical and Physiological Lectures, in which the several parts

on his curious collection of Anatomical waxworks, and other natural preparations; to be continued the whole winter until the course is completed. As this course cannot be attended with the disagreeable sight or smell of recent disease and putrid carcases, which often disgust even the students in Physick, as well as the curious, otherwise inclined to this useful and sublime part of natural philosophy, it is hoped this undertaking will meet with suitable encouragement.

Tickets to be had for the whole course at Dr. Chovet's house in Second Street, Philadelphia.

I cannot find whether these lectures were continued later, but at any rate, in 1793, the study of anatomy in Philadelphia; but it must be recognized that, though in one of the latest colonies to be founded, Philadelphia was then the metropolis of the

THE FOTHERGILL CRAYONS AT THE PENNSYLVANIA HOSPITAL ON WHICH SHIPPEN'S ANATOMICAL LECTURES WERE BASED.

his heirs sold the collection to the Pennsylvania Hospital as an important addition to their museum. At that time they consisted of eight wax models, ninety-three dried and sixty wet preparations.[27] Chovet's personal peculiarities and anecdotes about his jovial disposition have been so well described by Packard[28] and others that repetition here is unnecessary.

It may be thought that undue attention has thus far been paid to the progress of

country,[29] and led the other centers in medicine as it did in various other pursuits. That this is recognized by other than Philadelphians is shown by the following quotation from one of the most charming of our medical essayists,[30] lost to us, alas, in his prime:

Many (Massachusetts Doctors) went to London and Edinburgh, but more flocked to the Philadelphia school. The foundation of the Harvard Medical School in 1782 by no means

put a stop to those Philadelphia journeys, for it took many years to bring the Harvard School up to the Philadelphia standard. In those days, Philadelphia had this lead over Boston in the advantages it offered medical students, that it provided abundant clinics at the old Pennsylvania Hospital. At Harvard there was no clinic worthy the name. A few patients were shown weekly at the ancient Boston Almshouse, but the school proper was in Cambridge, a two hours journey from Boston then, and the instruction given in Cambridge was altogether didactic.

New York medical progress followed close on the heels of Philadelphia. In 1763 Dr. Samuel Clossy (or Clossey), a graduate of Trinity College, Dublin, who stayed in this country until driven out by the Revolution, gave a course of lectures on anatomy at King's College (now Columbia University), comparable to those started the year before by Shippen in Philadelphia. In 1768 a medical department was started in the same institution, with Clossey as Professor of Anatomy, and among others, John Jones, Professor of Surgery, and the celebrated Samuel Bard (the son of the afore-mentioned John Bard) as Professor of the Theory and Practice of Physic. To Bard, who was considered by Mumford to be with Benjamin Rush the two foremost medical figures of the century, is usually given the chief credit for the foundation of this School.[31]

Organized anatomical instruction in Baltimore began somewhere between 1760 and 1770 with the work of Charles F. Wiesenthal, a Prussian "Medicinae Practicus," who arrived in Baltimore in 1755.[32] In the rear of his house on Gay Street, he erected buildings for his school and dissecting rooms, in which many eminent practitioners were taught until his death in 1789. These buildings are still standing in 1922, and will soon have vis-a-vis, the Memorial Building of the Great War recently dedicated by Marshall Foch.

In spite of the advanced state of learning in the New England colonies, and the early start that we have seen made in "Anatomies" and post-mortem examinations, institutional instruction in anatomy seems to have lagged. An Anatomical Society composed of undergraduates, was known to have existed at Harvard in 1771 and to have been in possession of a skeleton, "but their demonstrations were confined to the dissection of appropriate animals," as the examination of a human body was then an extraordinary occurrence even with our most inquisitive anatomists.[33] The first public lecture on Anatomy in Boston was given by John Jeffries (of English ballooning fame) shortly before the outbreak of the Revolution, and it was not until the closing years of the Revolution that in 1782 a medical school was organized in Cambridge.[34] In September, the Corporation of Harvard College adopted the report on the formation of a medical school and on November 22nd appointed John Warren, Professor of Anatomy and Surgery. This he accepted on December 24th, but was not inducted into office until the next October, with Waterhouse as Professor of the Theory and Practice of Physic, and Dexter, a few weeks later, as Professor of Chemistry and Materia Medica. Warren held this chair (which had been founded in 1770 by Ezekiel Hersey with a gift of 1,000 pounds) until his death in 1815.

John Warren,[35] a brother of the Joseph Warren who was killed at Bunker Hill, had served with distinction in various positions in the early days of the Revolutionary War, and on July 1, 1777, when only twenty-two years old, was made Senior Surgeon of the newly established General Hospital in Boston, a position which he occupied until the end of the war. Here, in the winter of 1780, he gave a course of anatomical lectures and dissections to a group of students, physicians and scientific gentlemen, which was so successful that the Boston Medical Society voted that he "be desired to demonstrate a course of anatomical lectures the ensuing winter." This he gave, as well as a third course in

1782, to which the Harvard Seniors were admitted, so that, like his friend Shippen's earlier lectures in Philadelphia, these played an important part in promoting the formation of a Medical faculty at Harvard.

In 1779 Thomas Jefferson had secured a Professorship of Anatomy, Medicine and Chemistry at William and Mary College, which, with the foundation of the Dartmouth Medical School in 1797 by Dr. Nathan Smith, completes the list of eighteenth century medical schools in the United States.

No evaluation of these accomplishments would be correct without due recognition of the obstacles in the way of anatomical investigation in the eighteenth century and even later. For most of this period there was no legal protection for the dissector, and anatomical material was so scarce that it had, as in the home countries, usually to be obtained by "body-snatching." It has already been related how the bodies of executed criminals were occasionally turned over by the authorities for dissection, and Edward Warren tells how in the Boston of his father's time, the Governor, who had the disposal of the body, might assign it to the man's friends or to a surgeon, or permit the prisoner to make his own arrangements for the sale of his own body. This gave rise, in the case of Levi Ames, to a night expedition and a matching of wits that is amusingly described in Warren's life.[36] Before the existence of a Medical School or lecture room, "the back windows of the house were occupied with drying preparations of legs and arms, and other anatomical and morbid specimens, prepared by Dr. Warren, and forming the basis of the Warren Museum, afterwards in the Medical College."

Often more serious events resulted from the prevailing ignorance and horror of dissections. Thus the building in which Shippen's dissections were made was several times attacked, and the Doctor forced to conceal himself; and on one occasion, his waiting carriage was driven off by a shower of missiles and pierced by a musket ball,

while he made his escape through a private alley. "Several times he addressed the citizens through the public papers, assuring them that the reports of his disturbing private burying grounds were absolutely false and stating that the subjects he dis-
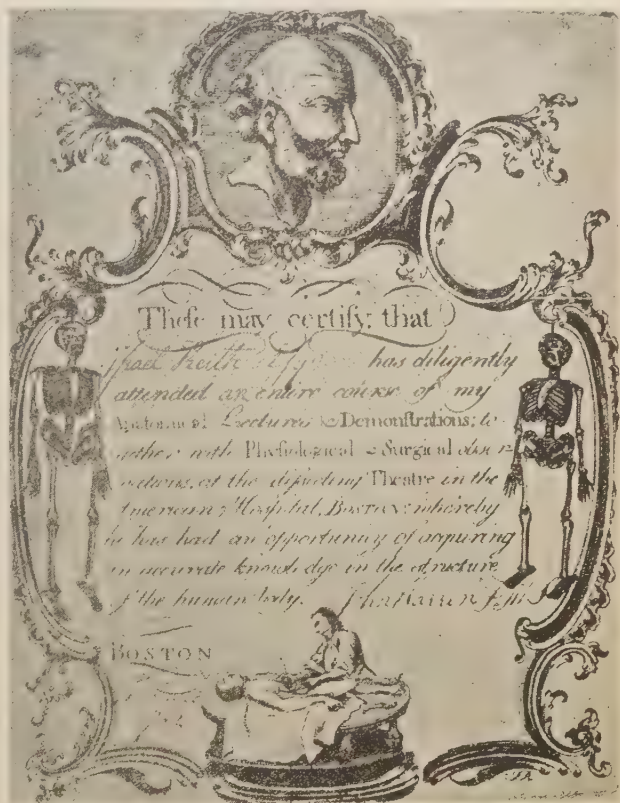
CERTIFICATE OF ATTENDANCE AT WARREN'S COURSE OF LECTURES, 1782, THE ORIGINAL OF WHICH WAS ENGRAVED BY PAUL REVERE.

sected were either of persons who had committed suicide, or such as had been publicly executed; except, he naively adds, 'now and then one from the Potter's Field'."[37]

In New York, the popular prejudice against dissection culminated in the celebrated Doctors' Mob of April, 1788. Doctor Richard Bayley, having waved the arm of a cadaver at a boy who was peeping through the window of the Society of the Hospital in the City of New York,[38] a mob collected which stormed the buildings, burned Bayley's valuable pathological collection, and attacked the jail whither the Doctors had fled. Seven rioters were killed and several more wounded before the disturbance was quelled by the militia. Probably

from this riot, however, came the first law to aid Anatomy, when New York, in 1789 made it lawful for the courts to add dissection to the death penalty in cases of murder, arson and burglary. In 1788 also, Wiesenthal's School in Baltimore was invaded by a mob, and the body of the murderer, Cassidy, which was being dissected, was taken from the gentlemen who were then studying anatomy and surgery.[39]

In 1778, the state of Virginia had stopped the dissection of executed criminals, permission for which had previously been a prerogative of the Royal Governors, and the Massachusetts Act of 1784 was apparently designed to discourage duelling rather than to protect anatomy. In it, the coroner was directed that he shall either bury the bodies of dead duellists "without a coffin, with a stake drove through the body ......
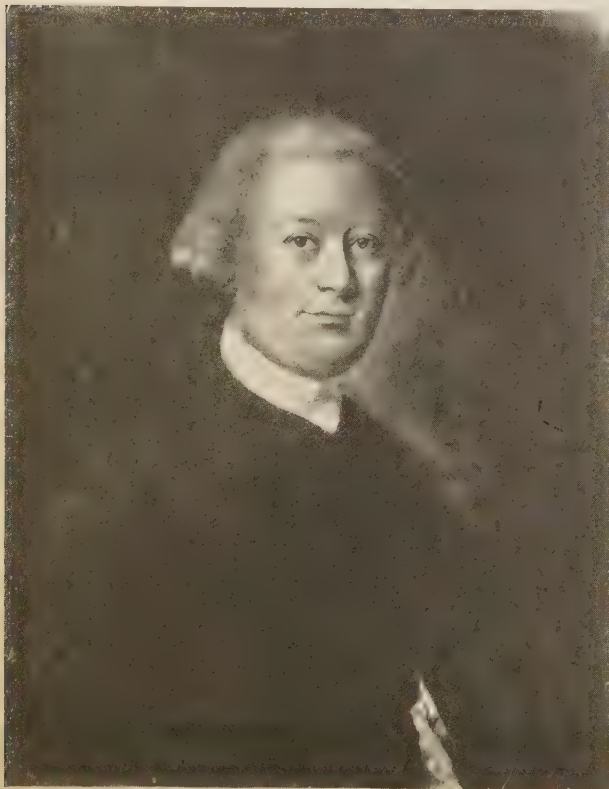
PORTRAIT OF WILLIAM HUNTER OF NEWPORT, R. I., PAINTED BY COSMO ALEXANDER, NOW IN THE POSSESSION OF A. F. HUNTER OF NEWPORT.

or shall deliver the body to any surgeon or surgeons to be dissected and anatomized." In 1790 the first Congress of the United States passed a law similar to the New York

law of 1789; but it was not until 1831 that any further advance was made, when Massachusetts authorized the delivery to the Anatomists of the unclaimed bodies of
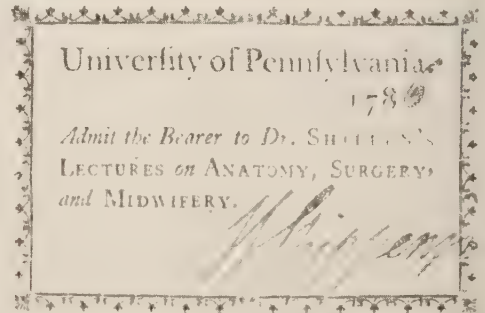
CERTIFICATE OF ATTENDANCE AT SHIPPEN'S LECTURES.

"deceased persons required to be buried at the public expense."[40] Even as late as this, however, coincident with the English "Resurrectionists," it is told that Dr. Beck had to drive a corpse from Albany to Boston, on account of the scarcity of anatomical material. In the State of Pennsylvania it was not until 1883 that a satisfactory law was obtained for the legal acquisition by an Anatomical Board of unclaimed and other bodies, for purposes of dissection and anatomical study. Since that time, however, there has never been any serious dearth of anatomical material, and with the gradual enlightenment of public opinion, the student has long been able to dissect to his heart's content without fear of mob violence. With an abundance of material and equipment, conditions for anatomical study in this country are therefore favorable. Although the steps of medical progress have inevitably, for the most part, left the firm footing of normal and pathological anatomy for more complicated and shifting fields, let us hope that the proper importance of these studies to the student beginning medicine will never be wholly lost sight of.

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the expedition that sailed from England on December 19, 1606, to found Jamestown (Toner's Medical Education in the United States, and Stith's History of Virginia, p. 48).

2. SAMUEL FULLER, medical practitioner and divine, who died at Plymouth in 1633, of a contagious disease caught from one of his patients (Toner, *loc. cit.*, p. 12).

3. SEBASTIAN CROL and JAN HUYCK came with Peter Minuit in 1626 (Walsh, J. J.: History of Medicine in New York).

4. THOMAS LLOYD, GRIFFITH OWEN and THOMAS WYNNE.

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6. The Clear Sun-shine of the Gospel breaking forth upon the Indians of New England, etc., by Thos. Shepard, reprinted in the *Coll. of the Mass. Hist. Soc.*, 1834, 3d s., iv, 37.

7. General Court (of Massachusetts) Records ii, 175, Session beginning October 27, 1647.

8. HARTWELL, E. M. Hindrances to Anatomical Studies in the United States. *Annals of Anat. and Surg.*, 1881, iii, 209.

9. Quoted by Hartwell, *loc. cit.*, from the *Pub. of the Mass. Hist. Soc.*

10. PACKARD, F. R. The History of Medicine in the United States, p. 63.

11. In a MS. Order of Council of Lord Baltimore dated St. Mary's in Maryland, July 20, 1670, John Stansley and John Pearce, Chyrurgeons, are ordered to view on Monday, August 8, 1670, the head of one Benjamin Price, supposed to have been killed by the Indians.

12. DR. JOHANNES KERFBYLE was a graduate of the University of Leyden, who came to New York about the time of the Dutch surrender. For the examination of the body of Gov. Slaughter, the six surgeons received £ 8,800, by order of the Council (Valentine's Manual of Common Council of New York, 1864, p. 590, quoted by Toner).

13. WALSH, J. J. The History of Medicine in New York, i, 37.

14. See DULLES, C. W. Life of Thomas Cadwalader. *Pa. Mag. of Hist. and Biog.*, 1903, p. 262, and Kelly and Burrage, American Medical Biographies, p. 189.

15. WISTAR, C. Eulogium on Dr. William Shippen, College of Physicians of Philadelphia, March, 1809.

16. The date 1750, that is sometimes given, is according to Dulles admittedly wrong, and in view of the preceding quotations, is much less probable than the earlier date.

17. An Essay on the West India Dry Gripes, to which is added an extraordinary case in physics. Printed by Benjamin Franklin, 1745.

18. Settlements in North America, quoted by Wickes, History of Medicine and Medical Men in New Jersey, Newark, 1871, p. 16.

19. Annual address to the Medical Society of the State of New York, 1811, quoted by N. S. Davis, History of Medical Education and Institutions in the United States, Chicago, 1851.

20. By photostat, from the copy in the New York Public Library.

21. KELLY and BURRAGE, *loc. cit.*, NORRIS, G. W. Early History of Medicine in Philadelphia, p. 209.

22. GARRISON, F. H. History of Medicine, p. 336.

23. These beautiful anatomical charts were made in 1755 by J. Van Riemsdyck, the artist employed by William Hunter to illustrate his work on the gravid uterus, from preparations made by Jenty, a well-known London dissector. As the crayons were made seven years before their presentation to the Pennsylvania Hospital, it is probable that they were a chance find, rather than done specifically for this purpose. Of the eighteen crayons, seventeen, recently reframed, now stand in the library of the Pennsylvania Hospital. The first of the series signed Burgess, though by a different hand, obviously belonged to the original lot. The eighteenth of the present set, an oil painting of the Love Sickness, has probably been included with the lapse of time to replace one that was lost. A recent cleaning, which revealed a figure of Cupid with bow and arrow in the background, furnishes its title. The crayons fall into three distinct groups; as two of these contain six and the other five, it is presumable that it is one of the stages of dissection of the whole body that has been lost. The three gypsum models of pregnancy now stand in the museum of the Ayer Laboratory at the Hospital.

24. MORTON, T. G. History of the Pennsylvania Hospital, 1751–1895; Packard, F. R., *loc. cit.*, and Scott, J. A., concerning the Fothergill pictures at the Pennsylvania Hospital, *U. of Penna. Med. Bull.*, 1904, xvi, 358. Another evidence of Fothergill's far-sighted generosity was his presentation to the hospital in the same year of An Experimental History of the Materia Medica, by William Lewis, F.R.S., 1761, "for the benefit of the young

students in physic, who may attend under the direction of the physicians." This proved to be the first book of the first institutional medical library in the country, which library had grown by 1790 to 528 volumes, and by 1857 to 10,500, and was probably during that period the best in the country.

25. The subject of his thesis, "De Placentae cum utero nexo," 1761, indicates already the bent of his activity.

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29. In 1790, with a total population in the United States of 3,928,326, Philadelphia had 45,250; New York, 33,131; Boston, 18,038; Charleston, 16,359; and Baltimore, 13,503. (Compiled by Toner from first U. S. census.)

30. MUMFORD, J. G. Medicine 100 years ago, in:
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31. WALSH, *loc. cit.*

32. CORDELL, E. F. Charles Frederick Wiesenthal, Medicinae Practicus, the Father of the Medical Profession of Baltimore. *J. Hop. Hosp. Bull.*, 1900, xi–xii, 170.

33. BARTLETT, Josiah. An Historical Sketch of the Progress of Medical Science. *Proc. Mass. Hist. Soc.*, 2s., i, 105.

34. HARRINGTON, T. F., and MUMFORD, J. G. History of the Harvard Medical School, New York, *Lewis Hist. Pub. Co.*, 1905.

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36. *loc. cit.* p. 228.

37. NORRIS, G. W. Early History of Medicine in Philadelphia.

38. This hospital was incorporated in 1771, and was also liberally helped by the afore-mentioned Dr. John Fothergill. Bayley, who like Shippen and others mentioned in this narrative, had also studied with William Hunter in London, later became Professor of Anatomy at Columbia.

39. GRIFFITH'S. *Annals of Baltimore*, quoted by Hartwell and Cordell.

40. HARTWELL, *loc. cit.*

WHEREAS ANOTOMY is allowed on all hands, to be the Foundation both of PHYSICK and SURGERY, and consequently, without SOME Knowledge of it, no Person can be duly qualified to practice either: This is therefore to inform the Publick, That a COURSE of OSTEOLOGY and MYOLOGY is intended to be begun, some Time in *February* next, in the City of *New-Brunswick*, (of which Notice will be given in this Paper, as soon as a proper Number have subscribed towards it.) In which Course, all the human BONES will be separately examined, and their Connections and Dependencies on each other demonstrated; and all the MUSCLES of a human BODY dissected; the Origin, Insertion, and Use of each, plainly shewn, &c. This Course is propos'd to be finished in the Space of a Month. By   THOMAS WOOD, Surgeon.

Such Gentlemen who are willing to attend this COURSE, are desired to subscribe their Names as soon as possible, with Mr. *Richard Ayscough*, Surgeon, at *New York*, or said *Thomas Wood*, at *New-Brunswick*, paying at the same Time, THREE POUNDS. Proc. and engaging to pay the said Sum of Three Pounds more, when the Course is half finished.

N. B. If proper Encouragement is given in this Course, he proposes soon after, to go thro' a Course of ANGIOLOGY and NEUROLOGY; and conclude, with performing all the OPERATIONS of SURGERY, on a dead Body: The Use of which will appear to every Person, who considers the Necessity of having (at least) SEEN them perform'd, before he *presumes* to perform them himself on any living Fellow-Creature.

THOMAS WOOD'S ANNOUNCEMENT IN THE *New York Weekly Postboy* OF JANUARY 17, 1752, OF THE FIRST COURSE OF ANATOMICAL LECTURES GIVEN IN BRITISH AMERICA.

ORGANIZATION AND FUNCTION OF THE NEW PATHOLOGICAL LABORATORY OF THE PHILADELPHIA GENERAL HOSPITAL

E. B. KRUMBHAAR, M. D., Director

The new Pathological Laboratory, although formally opened in December, 1919, on account of lack of necessary equipment and personnel, did not begin actual operations until the following July, since which time the routine work has already been more than double that of previous years. The Laboratory has been so organized as to give not only efficient service in the routine work demanded by the wards of a general hospital, but also to permit time for intensive investigation of such problems as are offered from time to time by the material at the disposal of the staff. To this end the work has been organized into the following divisions: 1. Clinical Pathology; 2. Bacteriology; 3. Biochemistry; 4. Postmortem Pathology. These are all under the supervision of the Director of the Laboratory (acting also as clinical pathologist), who in turn is responsible to the Medical Director of the hospital and through him to the Superintendent of the Bureau of Hospitals and Director of the Department of Public Health.

The Division of Clinical Pathology cares for most of the requests from the wards for the simpler laboratory tests, such as examination of urine, sputum, secretions, gastric contents, blood counts, etc. The work is done by three of the five internes on the laboratory service, aided by a technician, all under the supervision of the Clinical Pathologist and his assistant. During the course of the year they have performed over 30,000 examinations, and it is estimated that in the near future this amount will be almost doubled.

CARDIOGRAPHIC STUDY

The heart station for the cardiographic study of ward cases, although under the supervision of the Clinical Pathologist, is located in the Medical Division of the hospital, as it is necessary to bring all patients that are to be examined to the heart station. The electrocardiographer, assisted by a technician (both on half-time), are concerned with the graphic registration of the heart beat on all cases requested. This is done either with the Mackenzie polygraph, or more often with the string galvanometer, an expensive and stationary instrument, which, however, registers with extreme accuracy all disorders of mechanism of the heart beat. This is not only of great value in diagnosis and prognosis of heart disease, but furnishes valuable material for investigation in this important subject.

BACTERIOLOGY

The Division of Bacteriology is presided over by the Chief Bacteriologist, aided by two assistant bacteriologists, a serologist, and a technician, a cleaner, and an interne, all on full time. They are responsible for all the more complicated bacteriological requests, such as cultures from blood, and other body fluids and pus, for Wasserman tests, and other serological examinations; for the bacteriology of postmortem examinations, and of the milk and cream supply, and for occasional surveys of wards, clinics, etc., in the presence of epidemics, or persisting infections, as the occasion demands. Although all such examinations are necessarily more complicated and time consuming than in the Division of Clinical Pathology, they accomplish more than 10,000 reports annually, and already have undertaken several important investigations. Some of these will, of course, demand a long period before the results can be utilized, but in one at least it is probable that a valuable practical application will be made in the near future.

BIOCHEMISTRY

The Department of Biochemistry has been handicapped by our inability to secure a chief chemist. The staff, at present, consists of a full-time assistant chemist, a half-time

assistant, a technician and an interne. They perform the various tests in the chemistry of blood, urine and other body fluids, and in basal metabolisms, which are now so frequently demanded by progressive physicians. In addition they have frequent requests for reports on the chemistry of milk and cream supplied to the hospital, suspected cases of poisoning in the hospital wards, or occasionally at autopsy, and similar miscellaneous demands.

POSTMORTEM PATHOLOGY

The Division of Postmortem Pathology is under the immediate direction of the professors of pathology of three of the leading medical schools of the City, each serving for a period of four months. The autopsies are performed by their assistants, with the aid of the laboratory internes (serving in rotation), and of the morgue officer and his assistants. These pathologists serve without pay and utilize the material for instruction of the students in the respective institutions who come to this laboratory several times weekly for this purpose. The dictated descriptions of these autopsies are typewritten in triplicate by a stenographer, one copy kept as a permanent laboratory record in bound volumes, another sent to the hospital office to be bound with its clinical history, the third sent to the pathologist who performs the autopsy. The tissues taken for histological examination are prepared by two technicians, and examined by two histologists (on part time), and written descriptions in triplicate distributed in the manner before mentioned; or if from the nervous system by neuropathologists with their own technician specializing on this line. The histologists also examine all tissues removed at operations, which in many cases establishes a previously doubtful diagnosis, and is therefore of great value to both surgeon and patient. Appropriate specimens are handed over to the museum curator for proper preparation and mounting. It is hoped that with the 1,700 specimens now on hand, and the future accumulation rendered possible by the wealth of material, that this museum should become one of the most valuable in the country, both for exhibition and teaching purposes. Four anatomists are responsible for the proper cataloguing and description of these specimens, as well as giving needed assistance to the pathologist at the time of autopsy.

The five internes on laboratory service each spend two months in the laboratory, divided at present into twelve-day periods, of which periods two are spent on clinical pathology, one on urine examination, one on chemistry, one on bacteriology. This short time is barely sufficient to give them the practice in the routine of these branches that is demanded by the State Boards of Medical Examiners, and it is hoped that in the near future the time can be extended. The internes also rotate as assistants at autopsies, and on account of the wealth of material in this service, each interne acquires practical experience in the performance of from 10 to 16 autopsies. As it is emphasized to the chiefs of the divisions that the instruction of internes is a definite part of their duty, it is believed that this service is practically equivalent to a post graduate course on laboratory methods and will be even more valuable to the interne if the time could be prolonged. Including technicians, cleaners, and morgue officers, the total staff numbers 49, of whom 11 are unpaid, and many on part time, averaging from 3 to 5 hours daily.

The spacious quarters provided in the new laboratory will eventually not only give adequate space for the proper performance of the work indicated in the above outline, but also numerous research rooms to which it is hoped that graduate students or exchange workers from this or other cities will be attracted. The ample facilities which we hope soon to have installed, and the great mass of material afforded by the wards of the hospital, as well as the rapidly growing museum and library, shoulld afford many attractions to those desirous of undertaking the highest type of pathological study.

THE DEVELOPMENT AND USE OF INSTRUMENTS OF PRECISION IN THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

DR. THOMAS M. McMILLAN, In Charge, Cardiac Clinic and Electrocardiographer,
Philadelphia General Hospital

Heart disease has always ranked high as a cause of death. To-day it stands as the chief cause. Yet there is probably no other common disease or group of diseases, unless it be cancer, whose cause and mode of action has been less clearly understood or whose treatment has been so largely based on empiricism as had heart disease.

The revision of many of our ideas, and the advance in our knowledge of these conditions is quite recent medical history. Perhaps most of the recent ad-

ELECTROCARDIOGRAPHIC STATION—PHILADELPHIA GENERAL HOSPITAL

vances in our knowledge of heart disease have been brought about by the development and scientific use of instruments of precision. This development can only be considered here in a few of its phases.

The development of instruments of precision for the study of the heart may be said to have begun, in the modern sense at least, when MacKenzie undertook the study of the various forms of cardiac irregularity, conditions that had been responsible for many fanciful theories and explanations.

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As a result of his observations it occurred to him to make use of the arterial and venous pulsations. To record and study these, MacKenzie devised the instrument known to us to-day as the polygraph. Undertaking a previously baffling problem, and with only crude instruments of his own development, MacKenzie worked out an explanation of the mechanism of most of the forms of cardiac irregularity. In some cases, his original explanations were improved on by himself and others, yet his theories were in a large part correct; and his work stands to-day as one of the monumental medical achievements of recent times.

While MacKenzie brought to this problem admirable judgment and reason, yet it is fair to say that the development of the polygraph made possible his great findings.

EXAMINING ROOM, CONVALESCENT WARD AND HEART CLINIC—PHILADELPHIA HOSPITAL
FOR CONTAGIOUS DISEASES

The development of the electrocardiograph soon followed. Certain electrical changes that occurred in active muscle were already known. The principle of the string galvanometer likewise was known. It remained for Einthoven, the Dutch physiologist, to apply the string galvanometer for registering the electrical changes that occurred in the active heart muscle. With the advent of this instrument a new chapter in the study of the physiology and pathology of the heart began.

Sir James MacKenzie was quick to see the possibilities that this instrument offered and early advised Lewis, an associate of his at that time, to take up

this instrument and apply it to the study of the heart. This Lewis did, and it is he more than any other who has best used the unlimited possibilities of this instrument for the study of the heart in its normal and abnormal manifestations.

Not only has much been learned concerning the heart's action in its discorded arrhythmic states, but much has also been discovered concerning the physiology of the normal mechanism of the heart. Many of the primary and fundamental principles of cardiac action still remain questions. Even the cause of the heart beat is still a complex chemico-physical reaction about which we know little. The galvanometer and the study of the various electrical changes occurring in the heart is the method that holds out to us the greatest possibilities for the complete explanation of the mechanism of the heart's action. One of the most useful fields for the application of the galvanometric method lies in the study of the action of drugs on the various forms of cardiac function. Never before have we possessed so accurate and so delicate a method for the study of drug action on the heart. It is only just recently that we have come to have any accurate knowledge of the true effects on cardiac function of so universally used a drug as digitalis.

It is indeed an advance to see what might be called the synthetic principle applied in the field of cardiac therapy. To see the deliberate effort made to devise certain drugs or alter others in order to bring about certain desired effects, yet this is exactly what can be and is being attempted with the galvanometer to aid in determining minute and delicate responses.

The possibilities that the electrical method offers in the study of the physiology and pharmacology of the heart are limitless. However, not only is this instrument of great importance in research, but the greatest interest, perhaps, centers in the aid this method offers for the clinical diagnosis and treatment of heart disease.

As a practical adjunct to the clinician in the diagnosis and treatment of heart disease, it stands to-day as the instrument of precision that gives us the most minute and important findings. It has in no sense superseded clinical acumen. The interpretation and estimation of the cardiac state requires perhaps as much judgment and experience on the part of the physician as was required before the discovery of the galvanometer. It should be recalled that the diagnostic value of the galvanometer is distinctly limited. There are certain forms of heart disease in which the electrocardiographer yields no abnormal findings. A heart may be the seat of severe valvular disease and yet normal tracings may result. Persons may be dying with angina pectoris and no abnormality may be found in the graphic record. The diagnostic use of this instrument is limited in a large sense to that group of cardiac affections in which the electrical waves either pursue abnormal courses or have abnormal time relations. In other words, the arrhythmias and certain forms of myocarditis.

This group, however, is so large and so important, and the findings obtained by this graphic method are so clear, that this examination should form a part of the routine study of all cardiac cases. In many instances it gives us invaluable findings that are absolutely unobtainable in any other way. It will elucidate

many unusual forms of cardiac action that no other method of study will clarify. In spite of its limitations the recognized value of the electrocardiograph is so great that it now forms part of the equipment of every well-ordered hospital, and its graphic record forms a part of the routine study of all cases of heart disease.

Valuable as the findings of the galvanometer are, it has not superseded MacKenzie's polygraph. This useful little instrument has its place not only at the bedside, but in the laboratory as well. It is probable that from the point of view of diagnosis alone, the polygraph and electrocardiograph have reached the height of their development. It is doubtful if many new forms of cardiac arrhythmia will be found.

The field of advance that these instruments point to are the discovery and explanation of the various mechanisms and causes of the normal and abnormal types of cardiac action; the explanation of drug effects, and perhaps the development and discovery of new and more potent forms of cardiac therapy. In this field we may look with confidence for great advances.

THE PROGRESS OF SCIENTIFIC RESEARCH IN THE STUDY AND RELIEF OF HEART DISEASE

DR. EDWARD B. KRUMBHAAR, Director of Laboratories,
Philadelphia General Hospital

On the part of the lay public and of the medical practitioner who works twenty-four hours a day over the care of sick persons committed to his charge, there is naturally a not infrequent speculation as to the practical value of scientific investigation in medical affairs. Frequently the information sought after has little or no obvious connection with healing the sick, and when the further proposition is made that research should be encouraged even when the aim is admittedly without practical benefit, then lack of sympathy and understanding is even more to be expected; the latter position, however, is a perfectly proper one and to be encouraged by all means, as has been frequently shown in many branches of science, when the most important and far-reaching benefits have sprung from the most unlikely theoretical discoveries. The need for scientific research is each year becoming more widely recognized both in this country and abroad, and it is gratifying to feel, if one can judge by the number and amount of donations towards this end, that nowhere is this recognition more complete than in the United States. For instance, in our own City the recent appropriation by the City Council of two (2) grams of radium for the study and treatment of cancer was a step in the right direction, of which citizens of Philadelphia should be most proud.

Our knowledge of heart disease, like most other important branches of medicine, has been greatly extended in the present century and even in the last decade by the successful results of scientific research. The most important chapter, that of the contributions of the polygraph, electrocardiograph, sphygmomanometer and other instruments of precision, is described in Dr. McMillan's article in this BULLETIN. Suffice it here to say that this line of approach is still far from exhausted, and in the next decade may produce facts of even greater practical importance than in the past. The names of Gaskell, A. D. Waller, Wenckebach, Sir James Mackenzie, and Sir Thomas Lewis, the pioneers in this latest phase of cardiac study, will always stand high in the annals of cardiology.

In the last quarter century our knowledge of cardiac anatomy (one of the oldest branches of medical science) has, strange to relate, been very materially enlarged. In anatomy, more than in any other branch of medicine, it was felt that the important discoveries had been completed many years ago, and these recent additions are important examples of the ever-present need for research in medicine as in other sciences. The exact anatomical site at which the impulse of the heart beat normally begins was discovered by Keith in 1906, and the special muscle bundle that conducts the impulse from the auricle to the ventricle was first described by His in 1893 and rediscovered and first utilized in 1904. A few years later, Tawara discovered the muscle network that bears his name and the terminals which join this special conducting system to the ordinary heart muscle. Without this anatomical knowledge, the subsequent physiological

1

CARDIAC HISTORY—Subsequent Record

3

Hospital	Out-patient Dept. or Clinic No.		Issuing Clinic No.		Serial No. (A.P.R.H.)
Name of patient		Address		Age	S.M W.D.	M.F

Date				
HISTORY SINCE LAST VISIT				
IMPROVED—SAME—WORSE				
TIME LOST At home				
In hospital				
In convalescent home				
OCCUPATION				
CHIEF COMPLAINT				
SYMPTOMS Dyspnoea				
Cough				
Palpitation				
Precordial Pain				
Fatigue				
Sleep				
Bowels				
Appetite				
Rheumatic fever				
Twitching—Chorea				
Sore Throat				
Skin				
Nodules				
"Growing pains"				
Joint pains				
Fever				
Any new symptoms?				
GENERAL APPEARANCE				
Color				
Weight				
Height—Total—Torso				
Ear				
Nose				
Teeth				
TONSILS				
Operation				
Result				
Adenoids				
Tonsular nodes Right				
enlarged—Left				
LUNGS				
Vital Capacity				
HEART				
Rate				
Rhythm				
Thrill				
Cardiac outline in cm R Sp cm L.S. cm	R Sp cm L.S cm	R Sp cm L.S. cm	R Sp cm L. S. cm
Lower end sternum transversum cm. space	cm space	cm. space	cm. space
from midium line				
Sounds Base				
Apex				
Murmurs				
ARTERIES Thickened				
Pulse—Character				
Deficit				
B. P. Systolic Diastolic				
ABDOMEN				
Liver				
Spleen				
OEDEMA				
ELECTROCARDIOGRAM				
EXERCISE TEST				
X-RAY				
DIAGNOSIS—ETIOLOGICAL				
ANATOMICAL				
FUNCTIONAL CLASSIFICATION				
TREATMENT—Digitalis				
REMARKS				

History Record used by Heart Clinics in Philadelphia, reproduced from form used by the Association for the Prevention and Relief of Heart Disease, New York City

studies which have elicited so many various important new facts about the functioning of the heart would have been utterly impossible; and without these in turn, the important practical applications to the diagnosis, prognosis and treatment of heart disease would have been equally impossible.

By these means the whole field of irregular heart action has been mapped out within the past few years, so that instead of being content with the statement—almost universal a generation ago—that the pulse is irregular, we now can and should accurately determine which of six or eight forms of irregularity is present. Having learned that these different types of irregularity come from widely different causes, vary greatly in their gravity, and respond to different

RECREATION AND REST ARE FEATURES IN THE CONVALESCENT CARE OF PATIENTS—
PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES

forms of treatment (sometimes diametrically opposed), we are now able, thanks to the successful research along anatomical, physiological and pathological, as well as clinical lines of ten or twenty years ago, to care properly for this large and important group of cases.

From the middle of the Nineteenth Century, when important discoveries in pathology (i. e., the changes produced in tissues as the result of disease) were being made in the heart, great importance has been placed on the recognition of these changes during the life of the patient by the various means of physical

diagnosis. It remained for the scientific clinical investigators of the present century, however, to show that, important as the recognition of these changes may be, the functional capacity of the heart (*i. e.*, the working power of the heart muscle) is of even greater and paramount importance to the patients.

This conception was evolved and is still being impressed upon the medical public to-day by students of the heart as observed in animal experimentation and at the bedside. It is important to recognize that these two methods of approach go hand in hand, as indeed they have in cardiology since Harvey's discovery in the Seventeenth Century of the circulation of the blood, and that both are equally important to progress. New methods and new drugs must necessarily first be tried on animals before they can be used on man, and many valuable additions to our knowledge of heart disease would never have been acquired unless they could have been previously observed and tested on anesthetized animals. A recent example of an advance of this kind in the domain of pharmacology is the drug digitalis, which has been known as an important, if not the most important, heart remedy for over a century. It has only been within a few years, however, that the observation of its action on man and other mammals by instruments of precision (especially the electrocardiograph) has allowed a correct idea of how it works and, therefore, its more accurate and valuable use in heart disease. By means of the same instrument, the exact moment can be ascertained when the patient has had a sufficient amount of the drug, instead of waiting as previously for the later disagreeable clinical signs, such as nausea and vomiting. It might be thought by some that advances in knowledge coming from the bedside study of patients should not be included in the domain of scientific research, but nothing can be more fallacious. It cannot be too often emphasized that this correlation of bedside observations, if made with the proper care and accuracy, are as truly scientific investigations as are those of the erudite laboratory enthusiast working with the most elaborate apparatus and technique.

In the same way the various associations for the prevention and relief of heart disease, that have so recently been founded in Philadelphia and several other of our larger cities, should contribute materially not only to the actual relief of individuals but also to the knowledge of the underlying causes and factors of spread of heart disease, after which the practical application of the results of research by the removal or abatement of such causes should be a simple matter. The scientific collection of data by these associations, followed by its proper interpretation and the logical deductions therefrom, may easily prove to be the most important function that they will perform.

It can readily be seen that a detailed consideration of the progress of scientific cardiac research when such broad limits are assigned would be practically endless. If a few suggestive achievements and possibilities have been indicated, my present purpose will have been attained.

MEDICAL SOCIAL SERVICE RECORD

4

HOSPITAL	Outpatient Dept. or Clinic	Date	Issuing Clinic No	Serial No (A.P.R.H.)

NAME OF PATIENT	ADDRESS

OCCUPATIONS OF PATIENT

Name and address of employer	General nature of industry	Trade or particular kind of work	Type of work Heavy—Med.—Light	Taxing features:	Hours		Wage per week	How Obtained	Duration of Employment
					Days	Weeks			From — To
Present									
Subsequent									
Subsequent									
Subsequent									

HOME CIRCUMSTANCES.

Number in Family		Boarders	Lodgers	Family income weekly—				Weekly expenses			
Adults—16 and over	Children under 16			Total	Patient's earnings	From lodgers and boarders	Other	Rent	Food	Insurance	Other

THE HOME:

Tenement, apartment, private, furnished room boarding	Cleanliness: (Good—fair—poor)	Rooms: Number	Light—(yes or no)	Plumbing: Good—bad	Heat: (Stoves—steam—none)	Distance to nearest park	Roof available (Yes or no)

Cooking (Good—fair—poor)	Separate bed for patient (Yes or no)	Flights of stairs (a)—School (b)—Work (c)—Home	Referred from:	Referred to other organization:

MONTHLY REPORT

MONTH	Date patient Reported at Clinic	Clinic Report Classification	Working Yes or no	No. of days lost in previous month	Total earnings previous month	Idle? If so, why—state whether illness—unwilling —or no job available	Occupation changed State new trade	Patient's remarks:
January								
February								
March								
April								
May								
June								
July								
August								
September								
October								
November								
December								

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RETICULOSIS—INCREASED PERCENTAGE OF RETICULATED ERYTHROCYTES IN THE PERIPHERAL BLOOD*

By Edward B. Krumbhaar, M.D., Ph.D., Philadelphia, Pa.

THE presence of reticulated or "skeined" erythrocytes (hematies granuleuses) in the peripheral blood (as demonstrated by vital staining) has excited interest for many years, and in the last decade has assumed clinical importance as an index of the activity of blood formation. I would suggest as a matter of convenience that when the normal percentage of these cells in the peripheral blood is exceeded, the condition be designated "reticulosis," to replace some such expression as "an increase in the number of reticulated cells," as is now the custom. The word "reticulocyte" might similarly be substituted for "reticulated erythrocytes," but the term "reticulocytosis" (though perhaps more accurate etymologically) seems to me less desirable than the shorter and more convenient term.

In this paper I propose to consider the cytological status of these cells, and offer a few experimental and clinical facts pertaining thereto. Though now always studied by some form of so-called vital staining, they were almost surely first observed by Ehrlich[1] in 1881, in air dried blood smears stained with a saturated aqueous solution of methylene blue. To his credit it should be noted that at that time he considered them as not regressive. In using his method with preparations very freshly spread, I have seen the very fine network that he describes, but it is far less satisfactory than the use of vital staining.

Ehrlich's rather cursory observations were not followed up, although Pappenheim was working on the problem in the nineties.† With the beginning of the new century, however, hematological literature produced many observations and discussions on the nature of the various basophilic substances that are to be found in erythrocytes. The consensus of opinion resulting from these studies (though it must be admitted that but little conclusive proof has been brought forward) is that the reticulation indicates a protoplasmic substance (substantia granulo-filamentosa) and not a nuclear remnant, (being found well developed in nucleated erythrocytes and staining metachromatically with some nuclear stains) and that it indicates a young blood cell and not an old or degenerated cell. The reasons for the latter belief are that reticulocytes are found in great numbers in young infants and are rarer in adults, also that they are increased in those diseases in which there is an extra demand and an unimpaired source of supply (as in hemolytic

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†I have been unable to find this matter discussed in his inaugural thesis (Berlin 1895), to which references have been made. In a footnote on page 54 of an article in Virchow's Archiv. für Pathologische Anatomie, 1899, clix, he speaks of the use of thionin and neutral red as vital stains, but there is no mention of a reticulum in erythrocytes.

jaundice), and diminished or absent where the demand is lessened (as after transfusions) or if the bone marrow function is damaged (as in aplastic anemia). Stainability of the reticulum in many instances parallels polychromatophilia with the Romanowsky method. Enumeration of the polychromatophilic cells, however, cannot replace the reticulocyte count after vital staining, as the sharp distinction in the latter method does not exist in the former; also the former is not as delicate a method, so that very slight reticulations would be lost, and the count therefore always lower. That the two are not necessarily identical is shown by the fact that many polychromatophilic blasts do not contain reticulum, and that in combined staining, the two are not constantly associated.

The basophilic granules or "stippling," such as are found in lead poisoning, are usually considered to be of a different nature and probably indicate an abnormal or degenerated cell. The various nuclear remnants (Howell-Jolly bodies, etc.) belong, of course, to a different category. The very widespread distribution of mitochondria in the protoplasm of animal cells, together with certain similarities in behavior, has led to the assumption that the vital staining reticulum was the mitochondria of the young erythrocyte. Until this has been definitely proved, however, it would seem wiser not to confound the two terms, as is occasionally done; furthermore, Key[2] has recently acquired important evidence tending to show that the two substances are not identical. He calls attention to the fact that the reticulum differs from mitochondria, not only in morphology and various staining reactions, but also in its persistence after shedding, its resistance to heat and to solution by water, acetic and other acids, and alcohol, ether and chloroform.

METHODS

As the reticulum can be demonstrated in the erythrocyte by any method that introduces freshly drawn blood cells to any of the vital stains, and displays them suitably under the microscope, it is obvious that many different procedures will be advocated. Having been interested in these cells for a number of years, and tried various methods, we have found the following to be the simplest and most satisfactory for clinical use. A stock 0.3 per cent solution of Brilliant Cresyl Blue (Grubler) in normal salt solution, is prepared in quantity sufficient to last several months, filtered and kept in the ice box to inhibit molds. (Saturated aqueous solutions have also been used). Before using, it is diluted with four (4) parts of a 2 per cent sodium oxalate solution in normal salt solution to one (1) of the stock stain and in this strength is useful for several days. (If Grubler's stain is not available, a 1:2000 aqueous solution of Janus Green is recommended as a stock solution, and similarly diluted before using. I have not yet found an American-made Brilliant Cresyl Blue that is satisfactory, though no doubt such a one will soon be available.) From a free flowing cut, a drop of blood is sucked into a pipette and quickly diluted about 1:10 with the stain (for this purpose a leucocyte pipette is convenient, taking double the amount of blood customary for a leucocyte count). After standing 10 to 15 minutes, this is well shaken and a wet coverslip prepara-

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tion made from the contents, ringed with vaseline (to prevent drying and troublesome convection currents), and examined with the oil immersion lens. (Though for the most part easily visible in lower magnifications, some of the scantier reticula would inevitably be overlooked, unless the oil immersion is used.) This gives about 150 to 200 cells to a field, which can be reduced if desired by inserting a paper with a rectangular slit in the ocular. If reticulocytes are found to be frequent in the preliminary survey, the percentage is obtained by counting the number found in 500—or better 1000— erythrocytes, viewed in at least four different sections of the preparation. If rare—less than 1 per cent—truer results will be obtained if many more cells are examined, 10,000 or more. With good preparations, this can be done with reasonable accuracy by estimating the average number of cells per field, and counting the number of reticulocytes per field, until the requisite number has been examined. Especial care should be taken to prevent crenation, which makes the recognition of the reticulum more difficult and perhaps inhibits the entrance of the dye into the cell. If a permanent preparation is desired, more of the mixture can be spread on a slide, counterstained with a Romanowski stain, and mounted in the usual manner.

The above method seems to have some advantages over that of Vogel,[4] which has been advocated in some text books. It is not only simpler, but ensures a more representative sample. As the reticulocytes are said to have a different specific gravity from the normocytes, any method involving sedimentation would tend to introduce an error on this account.

A still simpler technic for clinical use employs a dry method with coverslips previously prepared with a dried film of the vital stain.[5] I have not found, however, that as high counts are obtained by this as by the wet method. In the haste necessary for making an even spread, it is possible that all the reticulocytes, and especially those with a very slight reticulum, are not properly stained.

The appearance of reticulocytes with Brilliant Cresyl Blue has already been so well described that it can be dismissed here with a reference to the accompanying sketch assembled from a slide prepared in the manner above described (Fig. 1). Attention should be drawn, however, to Key's observation that the form of the reticulum may vary greatly with the stain and method used, so that the familiar forms probably .do not picture the structure as it occurs in the unaltered cell, where it probably exists as a diffuse substance. We have also noted that the reticulocytes tend to be larger than the normocytes, and if the slide is allowed to stand, more of them become shadow cells than do the normocytes. This would appear to be contrary to the usual opinion that the younger reticulocytes are more resistant than the adult cells to changes in tonicity of the containing fluid. We have also observed that, even in preparations that are not overstained, some of the normocytes assume a greyish green appearance, much darker than the rest. Whether this indicates a significant tinctorial difference in these cells, or whether it is an artefact due to some other factor, such as difference in osmotic pressure, we

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are not in a position to decide. Metachromatic granules (staining red by this method) can occasionally be found.

EXPERIMENTAL RETICULOSIS IN ARTIFICIAL PLETHORA

An opportunity was offered to study the percentage of reticulocytes in dog's blood during the production of experimental plethora by means of daily transfusions from dog donors over periods of several months.[6] This is similar to but more prolonged than Robertson's[7] experiments with rabbits and has afforded somewhat similar results.

In four dogs studied in this manner, the reticulocytes either vanished entirely or diminished to such a point (considerably less than 0.1 per cent) that the possibility must be considered that those found had been introduced with the slightly anemic donor's blood. The curve of one of these dogs is shown in Table I. The temporary rise in the reticulocyte count immediately
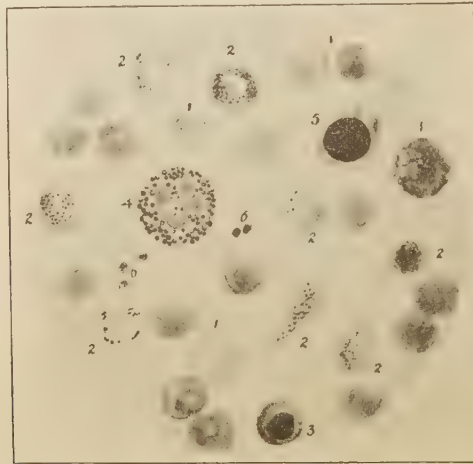
Fig. 1.—Sketch of selected blood cells, vitally stained with Brilliant Cresyl Blue; *1*, normocytes one pale, two others crenated; *2*, reticulocytes, showing granulofilamentous substance, appearing as a small or heavy network, or wreath; *3*, normoblast containing a reticulum; *4*, polymorphonuclear leucocyte, with highly refractile granules. *5*, lymphocyte with homogeneous nucleus and "glassy" protoplasm; *6*, blood platelets.

after transfusions were begun was found in another dog, and considered by us as probably due to bone marrow irritation.

A further record of the value of reticulocytes as an index of blood regeneration is shown in Table II, where dog 20-6, for reasons that we were unable to ascertain, developed a rapid and extreme hemolytic anemia six weeks after daily transfusions of 100 c.c. of whole blood had begun. Though the transfusions were continued without interruption, the hemoglobin count fell from 133 per cent (Newcomer) to 13 per cent in twenty-three days, and the erythrocyte count from 10,000,000 to 650,000 per cu.mm. After ten days, when the hemoglobin had reached 50 per cent, the reticulocytes began to increase and normoblasts and megaloblasts appeared in the peripheral circulation. The number of these fluctuated inversely with the hemoglobin count—the reticulocyte count being the more delicate and the more consistent—until after transfusions had been stopped, the reticulocyte percentage

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arose to the extremely high level of 81 per cent. With the gradual recovery from anemia, the reticulocyte count fell again until after four (4) months both curves had reached almost normal levels.

The only instance that I am aware of, in which such levels have been surpassed, is in Sappington's[8] rabbits made anemic with phenylhydrazine, where a reticulosis of more than 80 per cent was found in several instances and of 91 per cent in one instance, disappearing in ten days with return of the hemoglobin count to normal.

In dog 20-9 (Table I) a less severe anemia was present from the eighth to eleventh week, and during this period a mild reticulosis developed. It is to be expected that the degree of anemia at which the bone marrow will be sufficiently pushed to put forth an increased number of the relatively immature reticulocytes will vary considerably in different individuals and condi-
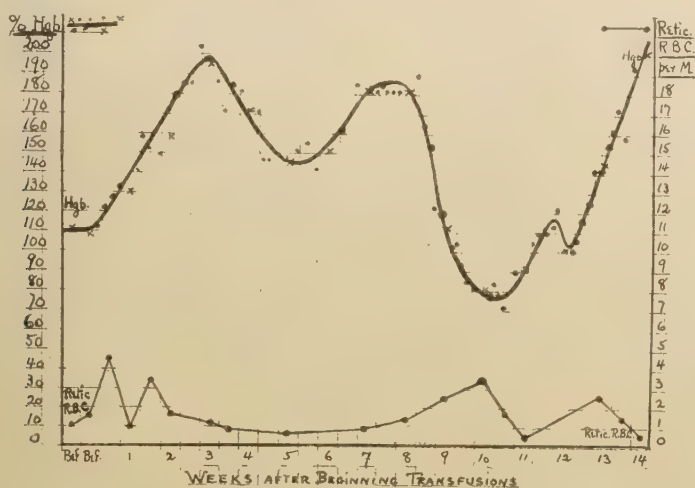
Table I.—Effect of daily repeated transfusions on hemoglobin and reticulocyte count. Dog. 20-9.

tions. With the continuance of transfusions the anemia in this dog was replaced by plethora and again the reticulocytes disappeared from the circulation.

NORMAL STANDARDS IN MAN AND LABORATORY ANIMALS

As I have not been able to find any statement of the normal reticulocyte picture in the common laboratory animals, Table III has been prepared to show the averages and normal ranges in normal animals living under customary laboratory conditions. It will be noted that, especially in rabbits, guinea pigs and mice, the individual variation is considerable, and it is quite possible that other individuals of a different strain and living under different conditions, would show still further variations. Lee and Minot[9] have placed the average for man at 0.8 per cent, and in Wood's *Chemical and Microscopic Diagnosis* and Emerson's *Clinical Diagnosis* (5th edition) even higher figures are given. This is distinctly higher than I have found in normal adults, (0.3 per cent) but in view of the individual variations, the matter is sufficiently covered for practical purposes, if initial counts are considered abnormal only

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if over 1 per cent or less than 0.1 per cent. Qualitatively it may be said that on the whole the reticulum tends to be large and heavy in the species that show the higher percentages. In the monkey it is especially delicate and feathery, while the human reticulocyte stands midway in these particulars, between those of the dog and cat, and those of the smaller animals.

RETICULOSIS IN INFANCY AND DISEASE

The average reticulocyte count for the normal human adult has been discussed in the previous paragraph. Statements as to the normal averages for
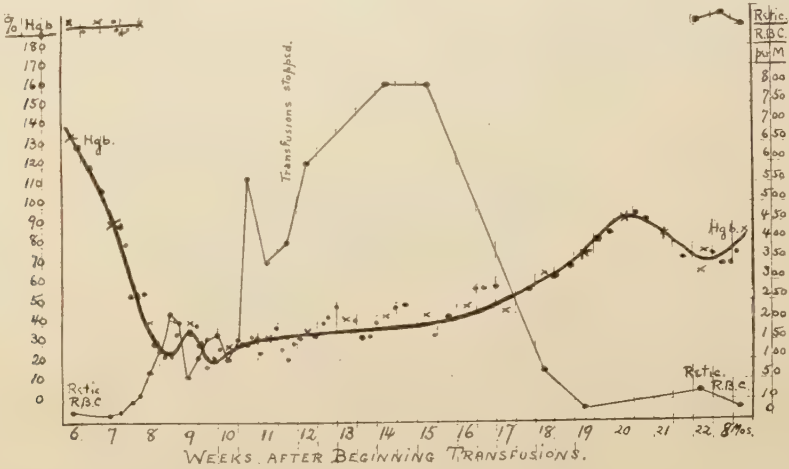
Table II.—Effect of daily repeated transfusions on hemoglobin and reticulocyte count, with supervention of anemia. Dog 20-6.

TABLE III

PERCENTAGE OF RETICULATED ERYTHROCYTES IN VARIOUS ANIMALS

SPECIES	AVERAGE	NORMAL RANGE
Man	0.3%	0.1—0.8%
Monkey	0.3%	0 —0.8%
Dog	0.6%	0.1—1.4%
Cat	0.2%	0 —0.4%
Guinea pig	3.0%	1.0—4.0%
Rabbit	2.0%	0.6—2.8%
Mouse	4.0%	1 —6.0%

infants, if given at all in text books of clinical pathology, are sufficiently at variance with the facts as I have found them easily to give rise to errors in diagnosis or prognosis. Thus it is usually stated that the average for normal infants is from 5 to 10 per cent, and even 20 per cent has not been considered abnormal. As will be seen in Table IV, I have not found any to exceed 5 per cent, or after the first twenty-four (24) hours to exceed 3 per cent. By the end of the first week, practically normal levels are reached, so that with these exceptions, the normal infant's reticulocyte picture is the same as that of adults. This roughly parallels the hemoglobin and erythrocyte curve for the same period. Cathala and Daunay,[10] the only others who appear to have studied the reticulocytes in early infancy, also found an increased num-

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ber at birth, which reached normal levels before the end of the first week. In eight infants they found from 11,000 to 360,000 reticulocytes per cu.mm. at birth; 25,000 to 155,000 the first day; 5,000 to 60,000 the second day; "very rare" by the seventh day; and (with the exception of one icteric) "very rare" by the seventh day. Allowing for the transient erythrocytosis that occurs during the first week of life, this would give a ratio of from 2 to 60 reticulocytes per thousand at birth, 3 to 20 per thousand the first day, 1 to 9 per thousand the second day; "rare" to 3 per thousand the fourth day; and less than one per thousand thereafter; i.e., distinctly lower figures than in our series. Reticulosis, on the other hand, in common with other hematological changes, develops more readily and to a greater degree in infancy after slight stimulus than during adult life.
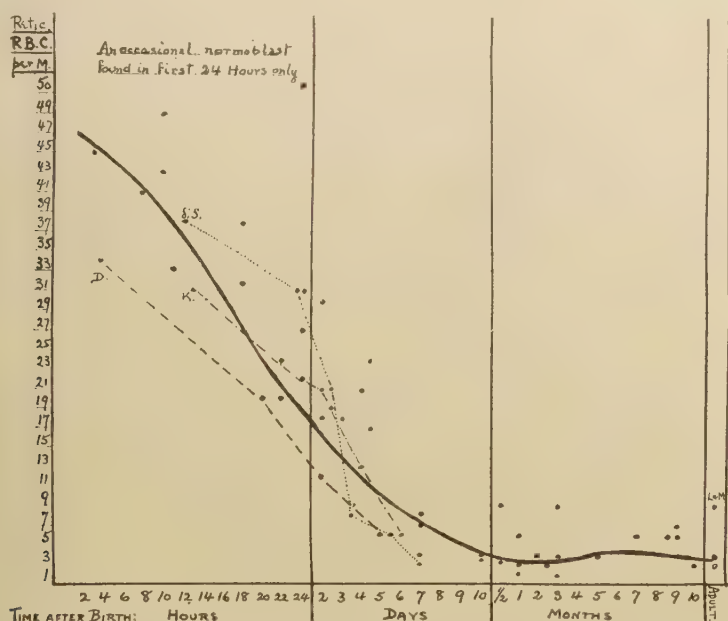
Table IV.—Curve showing number of reticulocytes per thousand during infancy. The solid line indicates the probable average curve; the broken lines denote a few characteristic individual curves.

Variations in the reticulocyte percentage in disease naturally depend on the intensity of the demand and the capacity of the bone marrow to respond. Thus is pernicious anemia, while there is usually a reticulosis of from 2 to 5 per cent, during "blood crises" or periods of remission, this may rise to 10 or 15 per cent; while in periods of regression these cells may be completely absent. In the two forms of hemolytic jaundice, the reticulosis is out of all proportion to the severity of the anemia, being customarily as high as 10 and even 20 per cent. The reason for this increase, which is of diagnostic import, has not been determined. In secondary anemias, the reticulosis may be said to be roughly proportioned to the severity of the anemia, and according to Christian,[11] it is also present in the purpuras. In true polycythemia they are also said to be increased, which would support the view that there is an increased demand for erythrocytes in this condition. In aplastic anemia and

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other forms of anemia due to decreased blood formation, these cells are diminished (reticulopenia) or absent.

SUMMARY

1. Erythrocytes revealing a more or less extensive reticulum (granulo-filamentous substance) by the methods of vital staining, may be conveniently designated "reticulocytes," and increase in their number is termed "reticulosis."

2. The reticulum is probably of protoplasmic origin, and indicates an intermediate stage between the erythroblast and the adult erythrocyte. A simple method for their recognition and estimation is described.

3. The greater delicacy of the tests for these cells and the greater constancy and delicacy of their variations in the peripheral blood, makes them more valuable criteria of the functional activity of the bone marrow than the study of polychromatophilia or nucleated forms.

4. In the blood of dogs made plethoric by repeated transfusions of blood, the reticulocytes diminished or disappeared entirely during the plethoric stage. With the occurrence of a hemolytic anemia, a reticulosis occurred, which in one instance reached 81 per cent.

5. The average percentage of reticulocytes and their normal range in man and the common laboratory animals is given.

6. The average curve of reticulosis during infancy is given, and the variations occurring in disease discussed.

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LYMPHOID METAPLASIA (HYPERPLASIA?) IN THE MAMMALIAN BONE MARROW *

E. B. Krumbhaar, M.D., Ph.D., Assoc. Prof. of Pathology, U. of Pa.
Graduate School of Medicine

(*From the Laboratories of the Philadelphia General Hospital.*)

The existence in the bone marrow of true lymph follicles with well developed germ centres, has been previously described by only three observers, and I have not been able to find any such observations in the pathological records of the three hospitals with which I have been associated.

Attempts today to explain satisfactorily their presence meet with several difficulties, among which may be mentioned the unsolved question as to whether or not lymphoid tissue normally exists there. If with Askanazy,[1] Weidenreich[2] and others, one believes that it does so exist, the presence of an unusual amount of lymphoid tissue or even of true lymphoid follicles can easily be explained as hyperplasia. If on the other hand with Ehrlich and Schridde[3] one adopts the more general view that no such tissue normally exists there, then its presence must be explained as due either to transplantation, to growth of embryonal remains, or to so-called metaplasia. A potent argument against the first of these theories is that the heterotopic follicles have always been found only in the one organ,

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while for our present purposes the various considerations will apply equally well to either of the other views.

The question of metaplasia, like so many other medical problems, has been considerably confused by the different constructions that have been put upon the meaning of this term — all the way from the mere replacement of one tissue by another, to the actual changing of adult cells from one type to another quite different type. The most useful conception is, I think, that expressed in Adami and McCrae's [4] textbook: "Metaplasia is the postnatal production of specialized tissue from cells which normally produce tissue of other orders and is an adaptation on the part of cells to an altered environment." Whether the metaplasia occurs through an anaplastic process of specialized cells to undifferentiated cells which then specialize along another line (Kataplasia) or whether the undifferentiated cells have been preëxistent in a dormant stage, is a matter of less importance. It is generally considered that in the above sense, metaplasia of epithelium from other epiblastic tissue and of bone from other mesoblastic tissue are the commonest forms, though it also occurs in other tissues of metoblastic origin.

In the closely related organs of the hemopoietic system, one might expect to find such interchanges, though in this case the question of proper terminology is further complicated by the uncertainty that exists as to the single, dual or plural origin of the various blood cells. No matter what one's views on this point may be, however, the principle might be considered the same and the application merely one of degree. Myeloid metaplasia of the spleen and liver has been described not infrequently, both clinically and in various experimental procedures. Donhauser's [5] case of anemia, due to chronic bone marrow sclerosis, affords a good example of such myeloid metaplasia in the spleen. See also Domenici, Arch. de med. et d'Anat. path., 1901, xiii, 1; R. S. Morris, Bull. Johns Hopkins Hosp., 1907, xviii, 200; R. Hertz, Fol. Hematol. Archiv, 1914, xviii, 219, and Zeitschr. f. Klin. Med., 1910, lxxi, 435; Tanaka, Ziegler's Beitr., 1912, liii, 338– (Literature in last two).
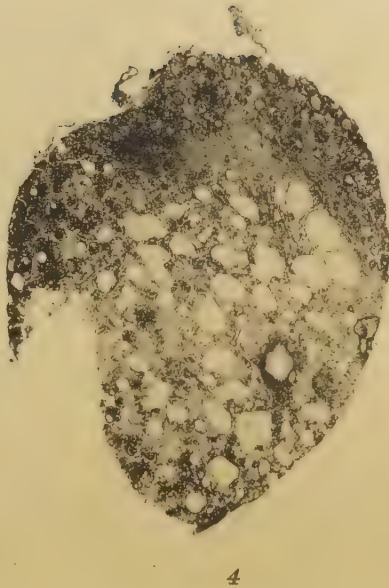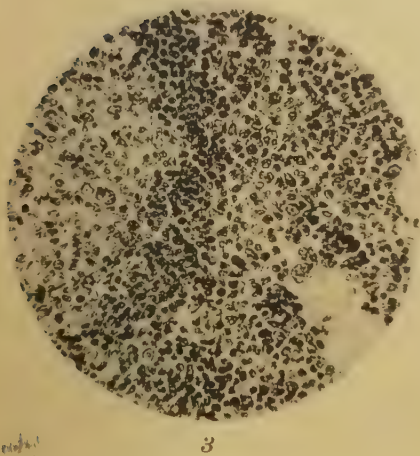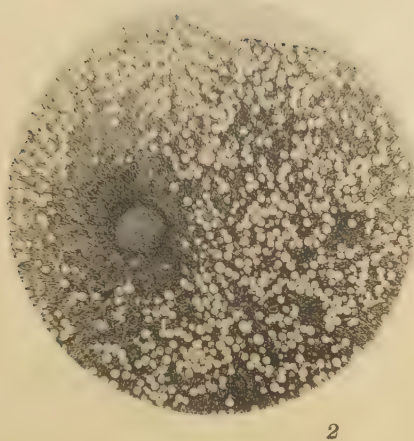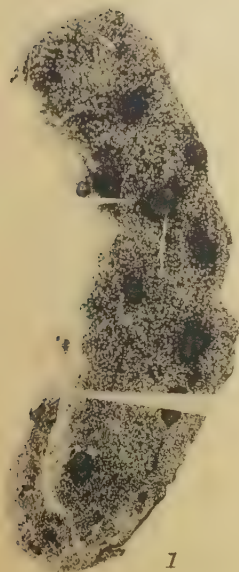
Krumbhaar.   Lymphoid Metaplasia.

The presence of lymphoid tissue in the bone marrow has been less frequently observed, and then usually in the form of small aggregations of lymphocytes (Dickson)[6]. Domarus[7] has reported an increase of lymphoid elements in the bone marrow following experimental anemia, and Hedinger[8] in a case of status lymphaticus associated with exophthalmic goitre, found the bone marrow studded with true lymphoid follicles, closely resembling those found in the present case. Askanazy[9] is one-hundred and twenty-six (126) persons dying at widely different ages, from miscellaneous diseases, found lymphoid tissue in the femoral bone marrow of forty-three (43). All of these aggregations, however, were less than 0.6 mm. in size, were infiltrated with myeloid cells and in only one was a germ centre found. The difficulty of determining lymphocytes under these conditions needs no comment. Oehme[10], on the other hand, studying chiefly children that had died from rickets, found lymphoid nodules in the bone marrow of twelve (12) out of twenty-three (23) examined, in most of which definite germ centres were described. It is unfortunate that no illustrations accompany either of these articles, as it is notoriously difficult, particularly in such conditions as Askanazy describes, to differentiate accurately between individual bone marrow cells. On the other hand, there is no doubt but that intensive studies such as these on many sections of bone marrow in a given case would throw more light on the activities of this poorly understood organ.

The present communication has to do with the finding of numerous lymphoid follicles with well marked germ centres in a healthy monkey, that had been submitted two (2) years previously to several experimental procedures.

Protocol. — M. Rhesus No. 5, weighing 2.2 kgms., one of a series in which the effect of splenectomy on the hemopoietic system was being studied, had his spleen removed January, 1920, and also some femoral bone marrow for histological examination. Both organs were later shown to be normal. His blood count, which had been normal before splenectomy, showed the usual transient leucocytosis and mild anemia.

On three occasions he was given toluylenediamine or sodium oleate, which only temporarily affected his blood picture and to a mild degree. In March, 1920, some abdominal lymph-nodes were removed, as a control operation, without any note-worthy change in the animal's condition. It was noted after this, however, that a distinct lymphocytosis developed and persisted till death, though whether it was due to splenectomy, nodectomy, both or neither, it is impossible to say.

In June, 1920, on account of the scarcity of material, he was used by Dr. Weidmann in his study of camphorated oil tumors. Camphorated oil was injected beneath the skin of the shoulders, a local procedure thought to be entirely with-out constitutional effect and limited to the site of injection and adjacent lymph nodes. The animal remained apparently healthy until he was chloroformed March, 1922, for purposes of histological study.

Autopsy. — General appearance and condition normal; weight 2.2 kgms. The omentum was adherent to one of the laparotomy scars and to the parietal peritoneum. No super-numerary spleens or structures suggesting hemolymph nodes were observed, but the great prominence of the lymph nodes (mesenteric, aortic, inguinal), was at once noticed. Many had beneath the capsule and on cut surface, a peculiar spongy or aerated appearance, that on histological examination was found to be due to the absorbed camphorated oil. A chain along the left iliac artery was especially noteworthy, being 4 cm. long, and containing some nodes more than 1 cm. in diameter.

The femur and femoral bone marrow showed no sign of the previous biopsy, except that the marrow of the right side was redder than the left (the side operated upon). On the right side the upper half of the shaft marrow was a uniform deep red throughout, the lower half reddish on the periphery of the cylinder, normal yellow in the centre. On the left side, the lower half was more reddish than the upper, though in both the hyperplasia was mostly in mottled areas. Nothing sug-gesting lymphoid follicles was observed grossly. Except for some anthracosis of lungs and bronchial lymph nodes, the other findings were negative.

Histologically, the bone marrow showed in all sections, in addition to the expected cellular hyperplasia, well marked, circumscribed lymph follicles with large germ centres. (Figs. 1–3.) The narrow ring of small lymphocytes merged sharply

TABLE I. — LEUCOCYTES AND DIFFERENTIAL COUNTS (MONKEY 5)

	Lcts.	Polys.	Lymphos.	L. & T.	Eos.
Before Splenectomy	15,600	8,700	5.700	900	300
" "	19,600	9,200	8,900	500	1,000

Splenectomy

1 Day after Splenectomy ...	24,300	22,000	....	....	....
3 " " "	16,200	6,800	8,200	1,200	....
28 " " "	14,800	6,000	7,800	600	400
8 Weeks " "	9,800	3,700	5,700	200	200

Nodectomy

9 Weeks after Splenectomy..	18,100	10,800	6,700	400	200
10 " " "	17,700	8,800	8,000	600	300
3 Months " "	17,100	9,700	6,800	400	200
4 " " "	16,800	5,000	11,400	400	....
5 " " "	12,400	2,800	9,300	300	....

Injection of camphorated oil

12 Months after Splenectomy.	31,000	22,000	7,100	1,500	400
15 " " "	22,000	8,800	11,700	1,100	400
24 " " "	26,000	9,600	11,400	....	5,000
25 " " "	18,600	3,700	14,000	800	400

Chloroformed.

into the surrounding hyperplastic bone marrow which seemed even more cellular here than in other parts, though distinctly hyperplastic throughout. In the germ centres were frequently found small pink staining areas, made up partly by acidophilic reticular cells, but more by closely associated connective tissue, similar to that frequently seen in splenic follicles. This

did not give the amyloid stain, and stained a pale blue with Mallory's Anilin Blue. It was taken as evidence that the follicles had existed for some time in the bone marrow. Central arterioles were very rare and then very eccentrically located. In most hyperplastic areas of the marrow, only a few fat cells were found per high power field; for the most part the cellular areas occupied slightly less than half of the total area. All the usual cells were found, but eosinophilic, myelocytes and leucocytes were much rarer than in Hedinger's drawing. Multinuclear giant cells were unusually prominent, especially in the neighborhood of the follicles. The leucogenetic series seemed on the whole to be the most increased and the miniature forms more so than the mature polys. Macrophages containing hemosiderin and extracellular hemosiderin were somewhat increased over the normal. Lymphocytes were only occasionally found and then not identified with certainty.

Almost all the lymph nodes showed the lesions characteristic of camphorated oil, namely tremendous endothelial hyperplasia, with vacuolization of the cytoplasm, larger vacuoles resembling fat cells and still larger round spaces, apparently containing globules of the oil itself, all staining red with Sudan III. Nothing unusual was found in the other organs.

The bone marrow removed at biopsy had a uniform reddish color, which was found microscopically to be due almost entirely to congestion. Small cellular areas showed the usual groups of bone marrow cells, with polys. and normoblasts the most prominent. There was a small amount of hemosiderin pigment present. The spleen and lymph nodes were normal.

Discussion. — The numerous lymph follicles in the bone marrow, when first seen microscopically, were suggestive of miliary tuberculosis. Special stains, however, failed to reveal any tubercle bacilli, and in no nodule was any necrosis or caseation observed. This, together with the facts that the monkey had been under observation, undisturbed and in good health, for almost two years; that there were no signs of tuberculosis elsewhere in the body; and that the nodules were identical with the lymph follicles of those nodes that were

undisturbed by the camphorated oil, all make it safe to believe that true lymph follicles and not tubercles were under consideration. Neither I nor the colleagues I have since asked have ever observed similar structures in the bone marrow, although in our studies on the spleen and on mustard gas poisoning, this organ received particular attention.

When one endeavors to account for the presence of the lymph follicles, it becomes impossible to do more than suggest various possibilities. The chance that it was a congenital anomaly is lessened by the failure to find any similar structures in the biopsy material, although it would not be impossible to miss widely scattered nodules even in serial sections of the small amount of tissue removed at operation. The lymphoid hyperplasia that has been so frequently reported after splenectomy of course must be considered as a possible cause, but in no other of our dogs or monkeys (a few of which have been allowed to survive an equal length of time), has such a picture ever been found, nor has it been reported in the literature. The unfortunate addition of the camphorated oil injections with the widespread change in the lymph nodes, must also be taken into account. In spite of the great enlargement of lymph nodes, the oil lesions constituted so great a percentage of the total, that a total lessening of functionally active lymphoid tissue is not out of the question. In fact, the most reasonable assumption seems to be that, due either to the loss of the spleen, or to the loss of lymphoid tissue from the camphorated oil lesions or to the nodectomies, or to all these causes, a need for further lymphoid tissue developed, which found expression in the metaplastic formation of lymph follicles in the related tissue — the bone marrow (or hyperplasia, if one believes that lymph tissue normally exists in the bone marrow). It is worth emphasizing that no other lymphoid hyperplasia was found in the liver or other tissues examined.

Summary. — 1. In a monkey that had undergone splenectomy and partial myelectomy and nodectomy, two years previously, and had received injections of camphorated oil shortly after, the bone marrow was found at autopsy to be

studded with lymphoid follicles, with well developed germ centres.

2. It is probable that these lymphoid follicles developed in response to a demand for more lymphoid tissue, as the result of one or more of the experimental procedures.

3. Whether this should be considered as hyperplasia, heteroplasia or metaplasia depends on more than one problem that still awaits solution.

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DESCRIPTION OF PLATE XII

Fig. 1. — Monkey's femoral bone marrow showing numerous lymph follicles with well developed germ centres. 48 mm., 4 x, magnification 9 x.

Fig. 2. — Same as Fig. 1, higher power. 16 mm., 15 x, magnification 46 x.

Fig. 3. — Right-hand portion of same lymph follicle in bone marrow, showing germ centre, narrow rim of lymphocytes and adjacent hyperplastic bone marrow. 4 mm., 15 x, magnification 76 x.

Fig. 4. — Cross section of lymph node, showing lesions produced by absorption of camphorated oil. 48 mm., 4 x, magnification 7 x.

RESIDUAL LACTATION ACINI IN THE FEMALE BREAST

THEIR RELATION TO CHRONIC CYSTIC MASTITIS AND MALIGNANT DISEASE

JOSEPH McFARLAND, M.D., Sc.D.

Professor of Pathology and Bacteriology, University of Pennsylvania;
Pathologist to the Philadelphia General Hospital

PHILADELPHIA

THE EVOLUTION AND INVOLUTION OF THE HUMAN BREAST

In the embryo of the lower animal, and in the human embryo of 8 mm., or less, a delicate line extends from the axillary to the inguinal region, along the junction of the abdominal wall and the membrana reuniens. It is known as the milk line, and consists of an epidermal thickening which later breaks up into ten or twelve nodal points, the rudiments of the future mammary glands.

In different animals a varying number of these glands persist and undergo further development, while the remainder disappear, so that, with the completion of development, each animal is provided with the number of mammary glands normal to its kind, and in positions in conformity to its type. H. Schmidt has shown that human embryos are provided with a somewhat variable number of these rudiments, although normally only two survive, situated on the thorax in the pectoral region.

In embryos of from 14 to 15 mm. the rudiments are composed of circular aggregations of epidermal cells dipping downward into the derm. Later each becomes divided into a number of segments, and the central cells, becoming cornified, are cast off. At that time the future mammary gland appears as a depression on the skin. During the next few months the cellular segments elongate and become more or less cylindric, so that there is considerable resemblance between the appearance of the mammary rudiment and that of a sudoriparous gland. This has led some to believe that the mammary glands are enlarged and modified sweat glands; but the definite manner in which their rudiments are outlined seems sufficient to show that they are special organs. At this time the epithelial cylinders are solid, and so they remain, penetrating more deeply and more widely as the fetus grows.

Immediately after birth, in both sexes, the central cells of the cylinders disappear by vacuolation, and they become hollow and almost immediately filled and later distended by a copious exudation of fluid in which more or less fat appears, either as free droplets, or as droplets enclosed in cells similar to, if not identical with, the colostrum cells of the adult breast before lactation.

This is the so-called "witch's milk." At the time it appears there are no acini, such as appear during lactation in the adult breast. The secretion seems to exude from the ducts, lining which are cells which may contain fat droplets. In the course of a few weeks, the secretion and the enlargement of the gland that accompanies it gradually disappear; the fluid is absorbed; the tubules contract and return to much the same condition as before the change occurred, except that the lumina subsequently remain distinctly patent. The parenchyma of this still rudimentary mammary structure is distributed throughout a seemingly dense fibrillar tissue beneath the skin.

At a time, varying from the twelfth to the seventeenth year, usually between the thirteenth and fifteenth years, the glands in both sexes undergo further development, with very little increase in size in boys, but with great increase in size in girls. The division of the parenchyma into segments or lobes can be observed in the latter. There are from ten to twenty of these segments or lobes, indistinctly separated from one another by intermediate bands of dense fibrillar tissue derived from the subjacent fascia, but so blended with the general connective tissue of the organ as to baffle demonstration by dissection.

The lobes, not definitely separable, have a pyramidal form, the bases at the periphery, the apexes at the center, where they converge at the future nipple. The parenchyma, at this time, consists of branching ducts, radiating from the nipple and distributed throughout the connective tissue.

At birth there is no nipple; instead there is a slight depression at the center of a circular area of modified skin, known as the areola. It is in immediate juxtaposition to this that the parenchyma of the future breast lies, and as it begins to grow at the time of puberty, the areola becomes elevated and projects in the form of a conical eminence. As the ducts continue to extend centripitally, and the stroma increases in quantity, the elevation embraces more and more tissue beyond the areola, the size increases, and a hemispheric shape is gradually assumed.

The hemisphere, however, remains surmounted by the small primitive cone so that the entire breast at this time is conical. In the darker colored races this is sometimes the final form of the mamma; but in

Caucasians there is a further change incidental to the appearance of muscular tissue about the nipple and backward traction of the fascia between the milk ducts. The result is flattening of the cone and the projection of the nipple. In the breasts of males the changes are much less striking, but there is increase of the parenchyma and development of a nipple.

Up to this time the breasts of both sexes are substantially alike, except that that of the female greatly exceeds that of the male in size and in the quantity of parenchyma. But what seems to be commonly overlooked is the fact that the breasts of both sexes frequently remain in this state of simplicity throughout the entire life of the individual unless some stimulus determines further development. On the other
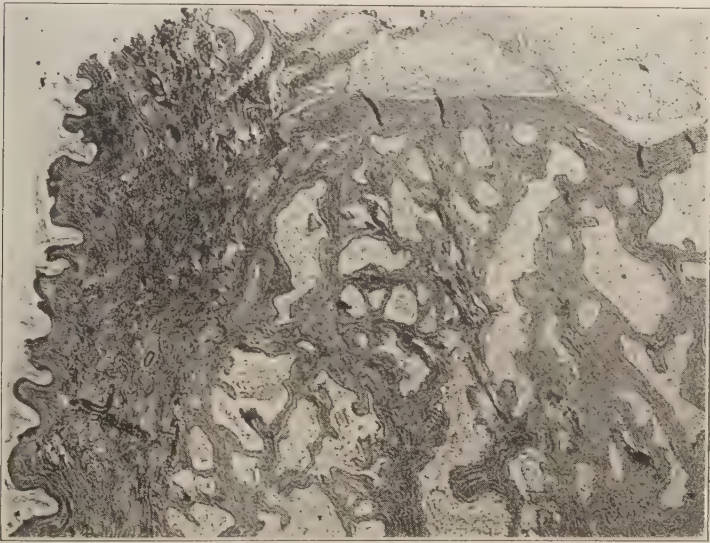
Fig. 1.—Necropsy specimen from normal breast of R. N., aged 3 weeks, showing the dilatation of the ducts by the "witch's milk." There are no lobules and no acini. The magnification is too low to enable the cells lining the ducts to be recognized. (From the Philadelphia General Hospital.)

hand, in many cases, at this early period, and for no discoverable reason, the breasts seem to assume a much more highly complex development with the formation of the well known textbook lobule.

So far as known this structure never makes its appearance in the male breast, and in those cases in which the male breast has engaged in milk secretion, it seems to be through the activity of the cells of the ducts, as in the infantile activity resulting in "witch's milk."

According to the descriptions in the textbooks, the lobule is the characteristic element of the parenchyma of the mammary tissue. It

is of interest, therefore, to find that there are many cases in which it is completely or almost completely absent. In the breasts of seventeen girls and women known not to have borne children, and ranging in age from 12 to 70 years, no distinct lobules were found. This at first led to the assumption that the breasts of women that had never been pregnant were continually without definite and well formed lobules, and so gave the impression that it was possible from the examination of the breast alone to discover whether a woman had been pregnant or not. This seems to be a mistake. Through the kindness of Dr. Joseph C. Bloodgood, an opportunity was presented to supplement the study of the series of breasts secured at necropsy with breast tissue surrounding benign tumors of the breasts of unmarried girls and young women, known not to have been pregnant, in many of which lobules were

TABLE 1.—Condition of the Parenchyma in the Breast of Women Known not to Have Had Children

Age in Years	Condition of Parenchyma
12	Ducts in small groups, no lobules
12	Rudimentary lobules, very small
14	Rudimentary lobules, very small
15	Rudimentary lobules, very small
17	A few well developed lobules (This girl had carcinoma of the other breast)
18	No lobules
21	Few well developed lobules of small size (The ovaries had been removed at 19)
26	No lobules
40	A few small rudimentary lobules
47	A few small rudimentary lobules
47	A good many large rudimentary lobules
51	Occasional small rudimentary lobules
53	No lobules
56	A few small rudimentary lobules
65	No lobules
65	No lobules
70	No lobules

present, some being well formed. The histologic structure of the virgin breast is therefore varied. For convenience of description it can be divided into parenchyma and stroma:

I. *The Parenchyma.*—In its most simple form the parenchyma consists of tubular structures that are easily recognized as ducts. In sections they may appear singly, or may be collected in groups. To the latter it seems appropriate to apply the term *rudimentary lobule.* They differ from the developed, or textbook, lobule through the absence of distinct periductal tissue.

The size of the ducts is variable; some are small, with very inconsiderable lumina; others are large, with widely dilated lumina. They almost always have distinct lumina, primarily because of the infantile secretion already referred to, and because of subsequent periodic activity of a secretory character. It is well known that young women not infrequently experience slight tenderness of the breasts at the time of menstruation, and some of them are at that time able to discover a

slight amount of moisture in the breasts. Others observe swelling of the glands, and a few are able to express considerable watery secretion. Rare cases are on record in which with each recurring menstrual period a distinct milky secretion has occurred.

The ducts appearing in the sections are not always empty. They are likely to contain more or less jelly-like material that probably results from the action of the fixatives on the proteins in the secretion which they contained; and in it there may be some admixture of fatty molecules.

The rudimentary lobules may be numerous and large, and may pass by imperceptible gradations into the atypical or textbook lobules which are characterized by the presence of abundant periductal tissue.
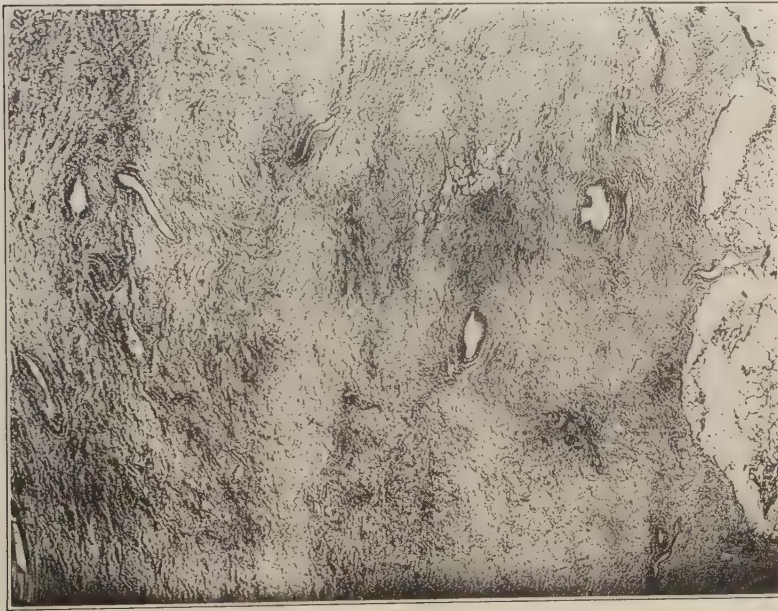
Fig. 2.—Necropsy specimen from normal breast of T. B., man, aged 38. The stroma of the breast corresponds to the perilobular stroma of the virgin female breast. In it only a few fat cells can be detected. The glandular parenchyma is represented solely by ducts, and the structure is identical with that found in the breast of the young virgin. (From the Philadelphia General Hospital.)

The structure of the ducts is simple, consisting of a basement membrane, not always easy to define on account of its thinness, and a single layer of cells. The appearance of these will vary according to the region from which the section is removed. If deep in the breast, the ducts are always lined with epithelium of cuboidal type; if near the nipple, by epithelium which becomes higher and more nearly columnar as the dilatations—milk sinuses—below the nipple are approached.

If a milk duct could be followed from its ending in the nipple to its beginning deep in the parenchyma, it would be found that the squamous epithelium of the outer skin dips a short distance into it, then suddenly changes to columnar epithelium, which continues a considerable distance, until the duct has divided several times, after which it gradually changes to cuboidal epithelium. As the fragments of tissue collected for the prosecution of this research were not intended for the determination of the structure of the ducts, they were taken from deeper portions than were appropriate, and observations on this point were merely incidental. Rugosity of the ducts was very common, as

Fig. 3.—Necropsy specimen from normal breast of M. W., colored girl, aged 12 years. The stroma is almost entirely composed of purely fibrillar, perilobular connective tissue. Extending from the lower edge of the section toward the blood vessel, to the left of the center, there is some interlobular connective tissue. The parenchyma consists solely of ducts and minute rudimentary lobules, one of the former being conspicuous to the right of the center, one of the latter is in the upper left corner. There was no fat in this breast, though it was quite shapely and well developed. (From the Philadelphia General Hospital.)

might be predicted from the frequency with which they are subject to distention and contraction with the variations of secretory activity.

From the rudimentary lobules composed of congeries of small ducts, without the number of tubular structures and the connecting periductal tissue characteristic of the classical lobule, one passed, in the series of cases studied, imperceptibly into the latter. That is, there were cases with no parenchymatous structures other than ducts, cases with rudi-

mentary lobules, cases with rudimentary lobules of large size, cases with large and small rudimentary lobules and small classical lobules, and cases with many large classical lobules.

So far as could be determined, there was no difference between the lobules in these virgin breasts and those in the mammae of parous women, so that the presence or absence of lobules does not form a means of determining the virginal state of the breast. The consideration of further particulars of the histology of the lobules themselves will be postponed until the history of the mammary lobule is described.

But here it must be pointed out that the development of the breast at the time of puberty, as well as later, and its extreme development at

Fig. 4.—Necropsy specimen from normal breast of L. D., white girl, aged 12 years, showing rudimentary lobules in the virgin breast, as well as the peri-lobular connective tissue above them and near the two opposite diagonal corners, the interlobular connective tissue which contains a few fatty deposits. The perilobular tissue is purely fibrillar in character. (From the Philadelphia General Hospital.)

the time that it is preparing for lactation, can only be accounted for as depending on certain stimuli. If these are efficient, the breast develops irrespective of everything else.

Of the nature of these stimulants nothing need be said here, the subject is physiologic, and is sufficient to fill a good sized paper in itself; but with respect to the response to stimuli, it is necessary to point out certain things at this point. In certain cases the stimulus may be excessive and come early, so that the growth of the breast at puberty does not cease at the development to the usual size, but continues to

an enormous size—puberty hypertrophy. Again, there are numerous cases in which the puberty hypertrophy is followed by the attainment of the normal size, but the occurrence of pregnancy is followed by the excessive development—pregnancy hypertrophy. Then there are still other cases in which for no discoverable reason the breast develops excessively, sometimes uniformly and on both sides, sometimes only on one side—nondescript hypertrophy. But what is of more interest now is the fact that the growth may be limited and localized, and therefore not referable to endocrine substances reaching it through the blood, but apparently dependent on local conditions resident in the breast itself. Such seemed to be the case in numerous of the sections shown by Bloodgood taken from tissue surrounding benign encapsulated
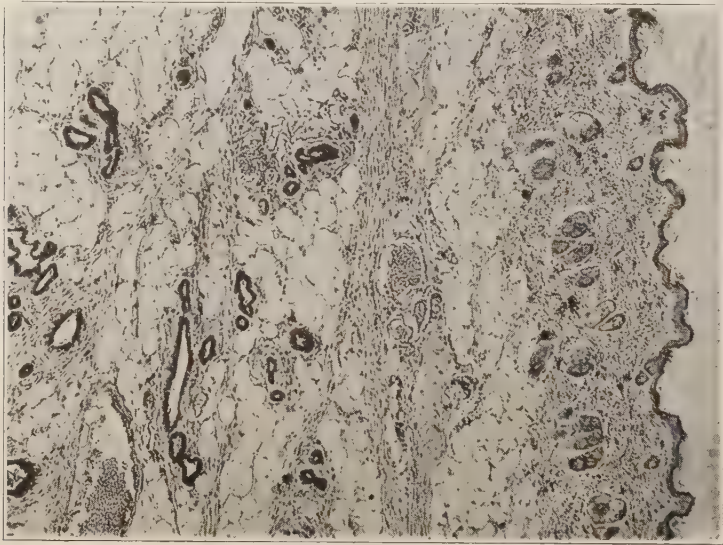
Fig. 5.—Mammary gland of virgin rat. The animal was three-fourths grown and in fine breeding condition; but it had been kept from the males. There are no lobules; the parenchyma of the gland is composed solely of ducts.

tumors in young women and girls. The appearance of the mammary tissue differed according to the proximity of the tumor. Away from it, the breast had a composition like that of the virgin breast already described; but as the tumor was approached, the lobules became larger and larger, until many of them appeared exactly like those of a breast that had recently been lactating. Unfortunately, there were no sections available from other parts of the breasts of these subjects from which it could be determined whether this development of the lobules was as local as it seemed, or was to be found in parts of the breast remote from the tumors.

From several of the sections it was difficult to come to any other conclusion than that the general structure of the breast was composed of a parenchyma made up of rudimentary lobules, which increased in size and development as the neighborhood of the tumor was reached.

But regardless of such local conditions as may play a part in their development, and of unusual stimuli governing their occasional maturation, it is pregnancy that is the great determiner of lobular growth and development in the breast, and to it I shall return later.

II. *The Stroma.*—To the palpating fingers the normal breast is soft but lacking in uniformity. It is hard to describe the exact sensation, but it is commonly said to be "corded," the source of the inequality being referred, by some writers, to the presence of vessels and milk
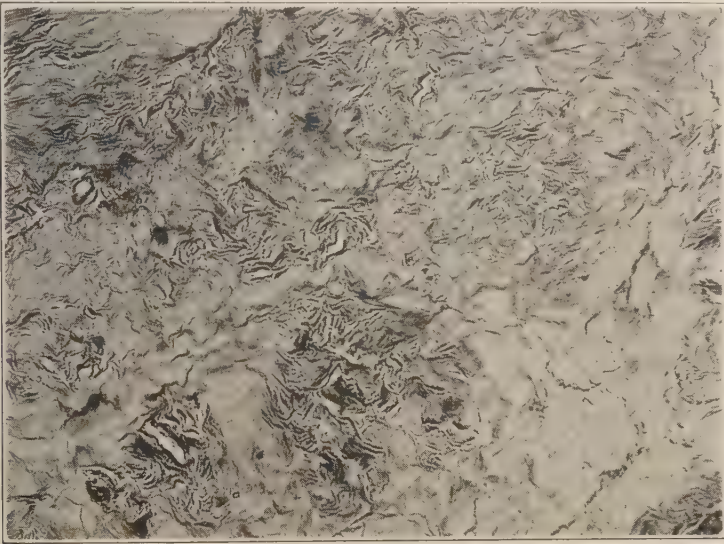
Fig. 6.—Necropsy specimen from normal breast of J. S., white woman, aged 22, showing the mucinoid stroma, as well as the fibrillar structure of the juvenile mammary gland. There is no fat in the perilobular tissue shown.

ducts. It is obvious that this is a mistake. Vessels are few and deeply seated. Milk ducts are also centrally and deeply seated, and their delicate structure makes it impossible to feel them. The real source of the inequality is the structure of the stroma which is peculiar both in quality and in distribution. It is primarily and fundamentally fibrillar, and may be divided as follows:

1. Interlobar Connective Tissue: This seems to be derived from the pectoral fascia, and extends upward, dividing the whole substance of the gland into the lobes already described. In it a varying quantity of adipose tissue is present. The general fatness or leanness of the

body seems to have little to do with the quantity of adipose tissue in the breast, however. The breasts of some lean women contain a great deal of fat and are large in consequence; those of some fat women contain very little fat and are small in consequence. In the breasts of one very fat woman, in our necropsy series, there was scarcely any adipose tissue.

2. The Interlobular Connective Tissue: This extends throughout the entire mammary tissue between its lobules, or in the case of virgins, between the potential lobules represented by the ducts and rudimentary lobules. In it occasional fat vacuoles may be found at any age, but fat regularly begins to appear as age increases. This is not a fixed rule, but it applies well in averaging the cases, with respect to both virgins and parous women, as will be evident by comparing the accompanying tables showing the conditions of the stroma in parous and nonparous women.

TABLE 2.—MICROSCOPIC STRUCTURE OF THE STROMA OF THE BREAST IN PAROUS AND IN NONPAROUS WOMEN

	Number of Cases Studied	Average Age of Women, Years
1. Nonparous women	17	36.7
Stroma fibrillar only	6	24
Stroma fibrillar and mucinoid	4	42
Stroma fibrillar, mucinoid and fatty	3	50
Stroma fibrillar and fatty	4	39
II. Parous women	124	46.2
Stroma fibrillar only	11	32.7
Stroma fibrillar and mucinoid	62	42.6
Stroma fibrillar, mucinoid and fatty	48	52
Stroma fibrillar and fatty, mostly fatty	3	58
Among the nonparous women the stroma was mucinoid in		41.17 per cent.
Among the parous women the stroma was mucinoid in		88.7 per cent.
Among the nonparous women the stroma was fatty in		41.17 per cent.
Among the parous women the stroma was fatty in		41.12 per cent.

It is thus seen that though there may be considerable adipose tissue in the interlobar tissue of the breast in youth, not much is to be expected to appear in the interlobular tissue until after the menopause. This may have an important bearing when it is remembered that in excising fragments of breast tissue for microscopic examination, the interlobar fat which is immediately visible is usually avoided in favor of the white tissue of the breast itself, which consists in large measure of the interlobular tissue.

Since the adipose tissue is so unequal in its presence and distribution, it cannot be to it that the breast owes its softness; the organ is soft, though firm in youth when very little fat is contained in its substance, soft and flabby in old women, when much fat is present. The fibrillar breasts of youth are protuberant; the fatty breasts of age, pendulous.

The interlobular distribution of the adipose tissue in the breast of young women and its interlobar and interlobular distribution in the breasts of older women may largely explain the inequality of the mammary tissue to which the "corded" sensation is due. The softness of the adipose tissue alternates with the firmer fibrillar tissue. But there is another factor of great importance in accounting for the soft consistency of the mammary tissue, that is, the mucinoid condition so common in its connective tissue. As has been shown in the tabulation, 41 per cent. of the breasts of nonparous women and 88 per cent. of those of parous women showed this condition in the fragments of tissue examined. It is quite probable that if greater areas of the breast
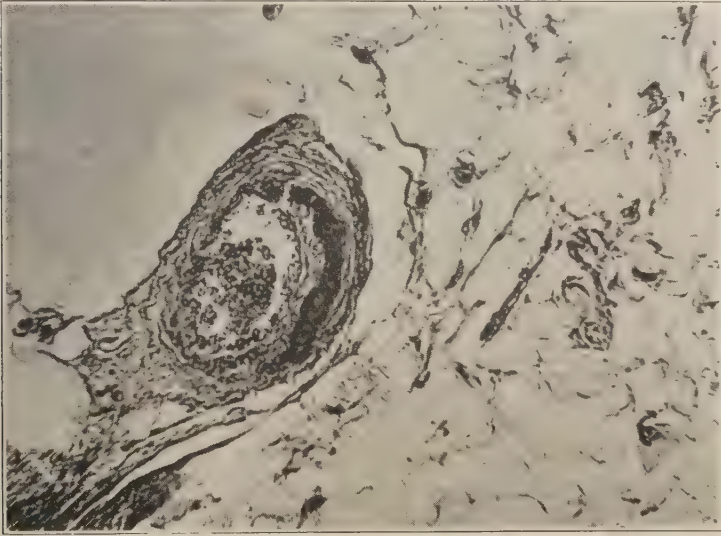
Fig. 7.—Necropsy specimen from normal breast of W. S., white woman, aged 81, showing calcification of the middle coat of a branch of the mammary artery. (From the Philadelphia General Hospital.)

tissue had been subjected to examination, a greater number of breasts would have shown it. Here is introduced a source of error that generally pervades the research. The breast is such a large organ that it is quite impossible to subject every part of it to microscopic examination; a supposedly representative sample is selected, and with what is seen in it one must be content, especially if a large number of cases are to be studied.

The change that is called mucinoid seems to result from some kind of softening of the collagen fibers of the connective tissue, which seem to lose distinctness and coalesce in a homogeneous mass through which capillary and other blood vessels and ducts are distributed and in

which lobules may lie embedded. At first it was supposed to be truly mucinoid, and like the gelatinous change so frequently seen in the tissue of tumors. But it fails to give the chemical reactions of the mucins, and it has not been possible to determine its true nature. It was at first looked upon as pathologic and possibly referable to disturbed conditions of the circulation, probably depending upon disease of the blood vessels. As will later be shown, disease of the blood vessels is of not infrequent occurrence in the breast; but it is impossible that the condition under consideration, which occurs in 88 per cent. of normal breasts and sets in after middle life with such regularity, can be so caused. It is sometimes found as early as the eighteenth year, and occurs in both virgins and parous women.

Fig. 8.—Necropsy specimen from normal breast of M. C., white woman, aged 53, showing a corpuscle of Pacini. It lies, as is usual, in the interlobular connective tissue, not far from the blood vessels. (From the Philadelphia General Hospital.)

It has, moreover, a somewhat regular distribution, occurring rather more frequently in the interlobular than in the perilobular tissue soon to be described. In some cases it occurs in the form of occasional fibers which, among those of ordinary appearance, show it through greater size and homogeneous appearance; sometimes whole strands of the fibers show it; sometimes great areas of tissue are so altered as to appear structureless and colorless or reddish from the eosin counter-stain.

3. The Perilobular Connective Tissue: This immediately surrounds the ducts and lobules in a more or less concentric fashion and seems

to be the last to undergo either the fatty or the mucinoid change. In many cases it is a distinct and easily recognizable tissue; but in others it is difficult to separate it from the interlobular tissue. It must be distinguished from the periductal tissue, which is intralobular, and will be considered with the parenchyma. Its distinctness is possibly due to the direction in which the section is cut. Should this be a fact it will serve to explain why in certain sections it is so distinct as to cause the section to be divided into many distinct entities, as the liver is divided into lobules, in the center of each of which there appears a duct, a small lobule. This perilobular connective tissue is destined to disappear in part or altogether when lactation hypertrophy occurs, and might, therefore, be expected to be of delicate structure and

Fig. 9.—Necropsy specimen from normal breast of M. M., white woman, aged 25, eighth month of pregnancy. The lobules have already attained a large size and many of the acini are dilated by beginning secretion, which also fills the ducts. (From the Philadelphia General Hospital.)

mucinoid character. That is, however, not the case; it usually appears dense. In all of these connective tissues there are collagen, fibroglia and elastic fibers, varying somewhat in quantity and in distribution according to the activities and metamorphoses through which the breast has passed in the course of a long life, including numerous pregnancies and lactations.

The stroma of the breast also contains vessels and nerves. Their presence depends upon the part of the organ from which the fragment for examination has been excised.

1. Arteries: These are usually small or of medium size, and are contracted. Occasionally, they show calcification of the middle coat, when they seem to lose their normal resisting power and undergo more or less dilatation. As usual, the calcification seems to be preceded by hyaline degeneration. No calcified vessels were found before the menopause. They were discovered at the ages given in Table 3.

2. Veins: The only change observed in the veins was dilatation, which seemed to be of frequent occurrence.

3. Nerves: Nerves were present in a number of the sections. Most of them were found unexpectedly; they were sometimes single and sometimes in groups. No pathologic alteration was noted in any of them.

The occurrence of the corpuscles of Vater, or pacinian corpuscles, was noted by Kölliker many years ago; but it is unusual to see them in sections made for pathologic study. It is probable that misinterpretations have arisen from their peculiar appearance and rarity. One

TABLE 3.—AGES AT WHICH CALCIFIED VESSELS WERE FOUND

Age in Years	Race	No. of Children	
47	Colored	2	
51	White	5	
55	Colored	?	
62	White	7	
66	White	?	
68	White	?	
70	White	?	
75	White	?	Hyaline degeneration
78	White	?	
81	White	?	
84	White	?	

was shown to a competent microscopist who after examining it critically suggested that it was a peculiar form of laminated thrombus. In the 150 cases upon which this research is based they were found eight times. Being normal and permanent structures, in all probability connected with the sensory system of nerves, the age at which they occur is of no consequence, varying from 16 days to 78 years. Like the nerves themselves the pacinian corpuscles are found in the interlobular connective tissue, near the larger blood vessels. They are large and striking objects, and not to be mistaken for anything else, by those familiar with them.

Except there be such obvious pathologic disturbances as suppuration, round cell infiltration, calcification or hemorrhage, the condition of the stroma of the breast seems to be a very insecure guide to the determination of the normality or abnormality of the organ, as it varies greatly according to the age, the sexual activity, and the individuality of the patient. Most of the breasts that come to microscopic study have been removed surgically, and taken from middle aged

women who have borne children. They present an appearance characteristic of that time of life and activity, with which all surgical pathologists become familiar. A breast from a virgin, many years younger, presents a very different appearance. In the former, there is likely to be a considerable admixture of fat, with corresponding diminution of fibrillar tissue; in the latter, there may be no adipose tissue, and much fibrillar tissue, a condition that is likely to be interpreted immediately to mean a pathologic condition of fibrosis, especially when the large amount of parenchyma in the former is compared with the very small amount in the latter, and the absence of lobules is taken
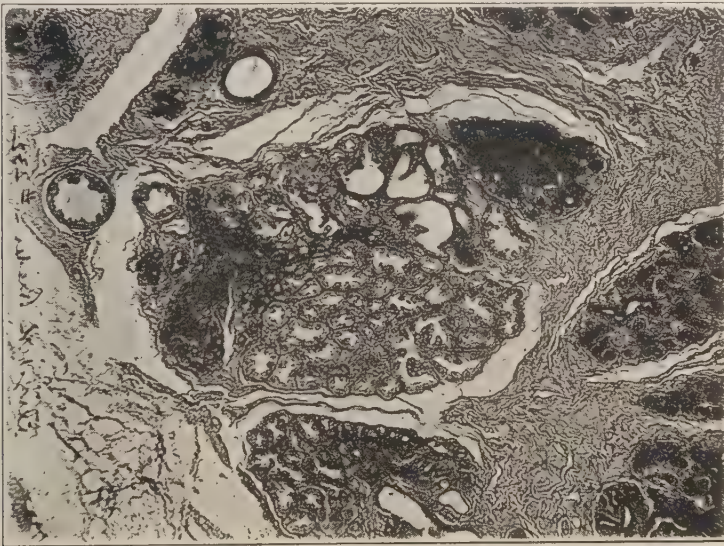
Fig. 10.—Necropsy specimen from normal breast of E. R., white woman, aged 23, who died of puerperal sepsis two days after the birth of her third child. There is great inequality in the size of the acini, some of which are entirely empty and contracted, others widely dilated, as in full lactation hypertrophy. (From the Philadelphia General Hospital.)

into consideration. It is suspected that the growth of the fibrillar tissue has resulted in the extinction of the lobules, when, as a matter of fact, there never were any there, and the presence of the fibrillar tissue is normal.

THE EVOLUTION OF THE BREAST FOR THE PERFORMANCE OF ITS FUNCTION—LACTATION

The great modifier of the mammary structure is pregnancy. It is with the occurrence of this state that the lobules invariably appear;

and after the menopause, when it is no longer possible, that they tend to disappear. Most of the subsequent history of the mammary gland has, therefore, to do with its lobules.

The History of the Mammary Lobule.—The starting point of the investigation should be the changes that occur in the breast of the primipara, and lead to the appearance of the lactation tissue. The rarity with which primiparous women die in the early months of pregnancy explains the first difficulty encountered—the inability to obtain the desired and necessary material. In our collection there were but two cases of very early pregnancy; but in each there had been prior pregnancies by which the conditions were so modified as to

Fig. 11.—Necropsy specimen from normal breast of M. M., white, aged 34, mother of six children, one of whom she was nursing at the time of her death The breast shows full lactation hypertrophy under low magnification. The perilobular tissue has disappeared and the interlobular tissue is represented only by fibrous partitions that support the blood vessels. The acini, which are somewhat collapsed because the secretion escaped when the tissue was cut, are of irregular shape and into many of them slender projections extend, like stumps of ruptured interlobular septums. Similar formations appear in the residual lactation acini. (From the Philadelphia General Hospital.)

make them valueless in answering the question of the early changes. In each the effects of the previous lactations were confused with those of the present one.

The observations, therefore, were begun with the study of the breast of a young primipara in the fifth month of pregnancy. At this time the increase of mammary parenchyma was astonishing; there

being a large number of lobules, varying in size from minuteness to a diameter great enough to fill an entire field under a low power magnification (Zeiss AA, ocular 4).

It is evident, therefore, that the mammary hypertrophy does not progress uniformly, but is more rapid in certain portions than elsewhere. Presumably, a study of the structure of the smallest of the lobules gives the best clue to the inception of the process. From these sections, it was determined that the hypertrophy of the parenchyma begins through budding from the ducts. In not a few areas there were small ducts, wrinkled and puckered, as though buds were
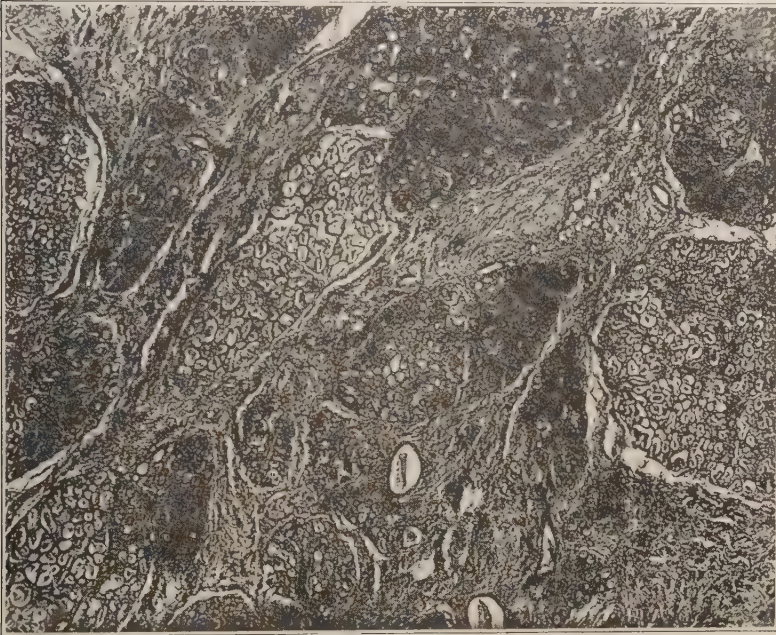
Fig. 12.—Necropsy specimen from normal breast of E. R., white woman, aged 23, delivered of a baby, Jan. 23, 1921, died of streptococcic puerperal infection a few days later in the Philadelphia General Hospital. The breast is in a condition of full lactation hypertrophy but no active secretion has begun. The quantity in the acini is not greater than it is in the earlier months of pregnancy. (From the Philadelphia General Hospital.)

growing out from their walls. From these, other smaller puckers were sometimes discoverable, as though secondary buds were forming from the primary ones.

At these points, there was no discoverable basement membrane, (The basement membrane of the parenchyma of the mammary gland is always difficult to define except in lobules long inactive.) The epithelial buds seemed frequently to be solid and composed of masses

of cells without differentiation. Through early vacuolation and fatty secretion by the cells, the centrally situated cells disappear, leaving lumina in the new formation. In this manner the parenchyma developed, acinus being added to acinus, and groups of acini collecting about the ducts and ductules. The acini first formed usually showed more or less secretion, which appeared in the sections either as jelly-like cylinders, or as collections of jelly mixed with fatty globules of considerable size.

There was another element of the parenchyma that merits attention —the intralobular or periductal connective tissue. The budding of the parenchyma scarcely begins before the growing ducts and developing

Fig. 13.—Necropsy specimen from normal breast of C. P., aged 28, white woman, mother of four children, date of last lactation not known. The greater part of the illustration shows parenchyma in the earlier nuclear stage of involution. The large lobule on the left has delayed its involution and its acini retain the lactation appearance. Such elements may evolve into residual lactation acini. (From the Philadelphia General Hospital.)

lobules are surrounded by broad areas of peculiar pale connective tissue, sharply differentiated from the perilobular tissue, and suggesting by its looseness and pallor an edematous condition. It is into this loose soft tissue that the budding parenchyma extends at first. But soon it seems to reach a point when it is no longer necessary for it to be preceded by this new formation, and it grows more rapidly than its associated connective tissue which seems to be lost by distribution. In breasts of women in the seventh, eighth and ninth months of preg-

nancy, periductal tissue is scarcely to be seen, the entire enormous lobules being composed of closely approximated acini. The dense, or seemingly dense, perilobular connective tissue is thrust aside in some manner, giving the impression that the growth of each lobule is like that of a benign tumor in which there is no peripheral infiltration, but only interstitial expansion. The perilobular tissue is not invaded and opened up by the acini, it is pushed aside and thinned more and more by the lobules, as they increase in size, until it is brought into juxtaposition with the interlobular tissue.

Secretion of fluid seems to begin almost as soon as the parenchyma begins to grow; but it is only after the fifth month of pregnancy that expression of fluid from the nipple is possible. The colostrum
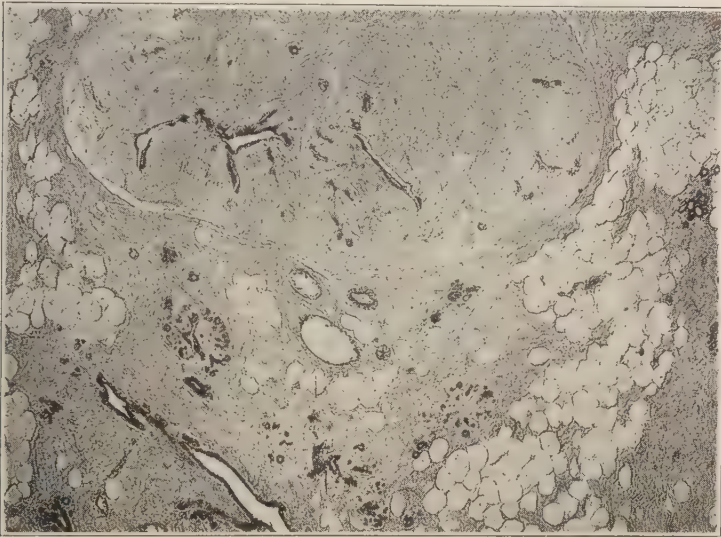
Fig. 14.—Necropsy specimen from normal breast of S. S., white woman, aged 19, died one year after having borne her first baby. The breast shows rapid involution. In the upper part of the illustration there is a large lobule almost entirely composed of periductal tissue. Below are several circumscribed lobules more nearly corresponding to the textbook illustrations. There are also several small uncircumscribed lobules. (From the Philadelphia General Hospital.)

cells seem to be the central cells of the newly formed acini, vacuolated by fat, or filled with fatty molecules that escape from the future acini as they are in process of forming lumina. They are relatively few in cases in which the secretion is scanty, and the lumen formation of the acini delicate, and many when there is much secretion and the lumen formation considerable. Sometimes quantities of them collect in the larger ducts. It did not seem possible that they were, as some think, leukocytes distended with molecular fat.

At the end of pregnancy, the quantity of parenchyma in the mammary glands varies greatly in different cases. In general, when compared with the quantity found in the breast of full lactation, it is surprisingly small, and gives the impression that lactation with adequate nutrition of the child would be impossible. There must be increase during the first few days postpartum, greater than anything that has gone before, probably through the new stimulus resulting from the application of the child to the breast. With the "coming of the milk" all of the newly formed acini dilate widely to an extent that seems to cause the rupture of some of their walls, as many of the larger ones have portions of interacinar septums sticking out like stumps into their spaces. The dilatation causes the partitions between the acini to

Fig. 15.—Necropsy specimen from normal breast of S. S., aged 19, white woman, showing an uncircumscribed and disrupted lobule following rapid involution. The patient had had a baby the year before she died. Fat cells can be seen in the interlobular tissue at the sides of the illustration. The periductal tissue can scarcely be recognized because of confused growth into the perilobular tissue. (From the Philadelphia General Hospital.)

become thin and the cells to be flattened. The flattening of the cells, together with the presence of many globules of fat in them, makes it difficult to determine the exact structure of the interacinar walls, with respect to the presence or absence of both mammary and basket cells. They are probably both there, the latter being compressed and difficult to see.

In full lactation hypertrophy, the periductal tissue disappears from view; the perilobular connective tissue can no longer be found, the

adipose tissue is completely absorbed and the interlobular connective tissue remains only as narrow strands separating large groups of lobules. Upon more careful observation in appropriate cases the outline of the lobules by the perilobular tissue can be made out, and gives an impression analogous to that produced by the outlining of the lobules of the liver of rodents by the bands of periportal connective tissue.

Thus the breast attains its full glandular perfection, and is transformed into a parenchymatous structure composed of lobules of fairly uniform size, closely approximated, and made up of newly formed structures, the acini. In this state it remains as long as the mother continues to lactate. With the weaning of the baby, the parenchyma ceases to be of further use; it seems by nature to be superfluous, and nature at once begins the process of getting rid of it.

TABLE 4.—Synopsis of the Microscopic Studies of Sixty-Eight Breasts of Women of the Child-Bearing Age

	Groups *				
	I	II	III	IV	V
No lobules in the sections	15	0	0	0	3
Lobules, large and numerous	0	3	9	7	0
Lobules, large, but few	0	1	0	1	0
Lobules, small	0	5	2	3	0
Lobules, vestigial—disappearing	0	5	11	3	0
Lobules, well circumscribed	0	3	3	2	0
Lobules, not well circumscribed	0	5	7	4	0
Lobules, uniform	0	1	1	1	0
Periductal tissue, conspicuous	0	2	4	0	0
Periductal tissue, not uniformly distributed in lobules	0	5	15	10	0
Periductal tissue, hyaline	0	1	0	0	0
Residual lactation acini	0	2	2	1	0
Microcysts	0	1	2	1	0
Large ducts, numerous	0	2	3	0	0

* Group I includes the breasts of women known not to have had children, microscopic confirmation; Group II, those of women known to have had children, microscopic confirmation; Group III, those of women known to have been married, microscopic evidences of lactation; Group IV, those of women in whose history there is no information as to matrimony or maternity, but whose breasts show microscopic evidences of lactation, and Group V, those of women with no history or microscopic evidence of lactation.

THE INVOLUTION OF THE BREAST AFTER LACTATION

It must, of course, be understood that the evolution of the parenchyma may miscarry anywhere along the line, and further development cease. Such a condition arises in cases of abortion, miscarriage, refusal on the part of the mother to nurse her child, the death of the infant at the time of birth, etc.

In these cases the breast ceases to evolve, but the occurrence of the pregnancy having been enough to initiate the formation of lobules, although incompletely developed, they at once begin the changes characteristic of involution.

The process of involution rarely proceeds uniformly and regularly, because all parts of the secreting breast are not uniformly active in secretion at the same time unless it is when the child is applied to

the breast and the maximum of secretory stimulation brought about. The examination of sections of breasts preparing for lactation and ceasing lactation will easily convince the observer of this, for in both cases there will be found in the same lobules of the mammary parenchyma a number of acini that appear of small size and are empty, and others that are distended with some kind of secretion. It seems as though the retention of the secretory function by some of the acini, and their distention by the products of that secretion interfere with the uniformity of involution. The varying degrees of interference arising from the varying conditions obtaining in different breasts cause remarkable differences in their microscopic appearance. In the same

Fig. 16.—Necropsy specimen from normal breast of W. F., married woman, aged 26, no history. (From the Philadelphia General Hospital.)

way, the differing conditions obtaining in different parts of the same breast, and the differing conditions obtaining in different parts of the same lobule, occasion dissimilarities in the histologic structure of different parts of the same breast, and of different parts of the same lobule. It is, therefore, not a simple, but a complex, series of events that characterize involution, with resulting different appearances, some of which prove very perplexing because their origin was not understood, and they have been misinterpreted by the best pathologists.

The mammary lobule is a temporary and transitory structure that usually exists in a rudimentary form before pregnancy occurs, and is destined to disappear after lactation is ended. The rapidity with which the lobules disappear varies greatly. In one breast of a young

woman, 19 years of age, who had had a baby one year before, there were a few small lobules fairly well conforming to the textbook description, while in the other breast there was scarcely a single one. The parenchyma had disappeared without distinct lobular formation, and with the most bizarre appearances of acinar and ductile vestiges, difficult to describe, but well shown in the illustration. On the other hand, the breast of a woman, 87 years old, still contained a few structures that could be recognized as vestiges of the definite lobules of long ago. It is necessary, though, to recognize rudimentary lobules in the virgin, fully developed lobules during lactation, decadent lobules during involution, and vestigial lobules after the menopause.

Fig. 17.—Specimen of normal breast from surgical case (A, B., white woman, aged 40), showing the typical textbook lobules that are supposed to represent the resting condition of the gland.

The general tendency of the mammary gland, therefore, seems to be to return to its virginal condition, and to contain nothing but ducts. The fulfilment of the tendency is, however, commonly interrupted by recurring pregnancies, and the complications interfering with involution to which reference has already been made.

Beginning with what seems to occur in cases in which involution takes place under most favorable conditions, and without complication, the sequence of events seems to be somewhat as follows. The acini of the lobule being empty, and no new secretion being produced to fill them, they yield to the pressure of the elastic tissue in their walls and contract to a smaller and smaller size until the lumen can no

longer be seen. At about the same time, the cytoplasm of the epithelial cells seems to shrink until it becomes difficult to see. In the meantime the periductal tissue which becomes visible again as the epithelial elements cease to preponderate over it in importance shows multiplication of its nuclei. The result is a remarkable nuclear appearance of the lobule, whose other elements have become so obscured that they are no longer recognizable. So similar are the nuclei arising in the periductal tissue and those of the decadent epithelial cells that it may be impossible to determine to what kind of cell a given nucleus belongs. The epithelial cells undergo progressive extinction, beginning, to all appearances, with those of the peripheral acini, and extending toward the ducts which persist as the alveoli of the classical lobule. With
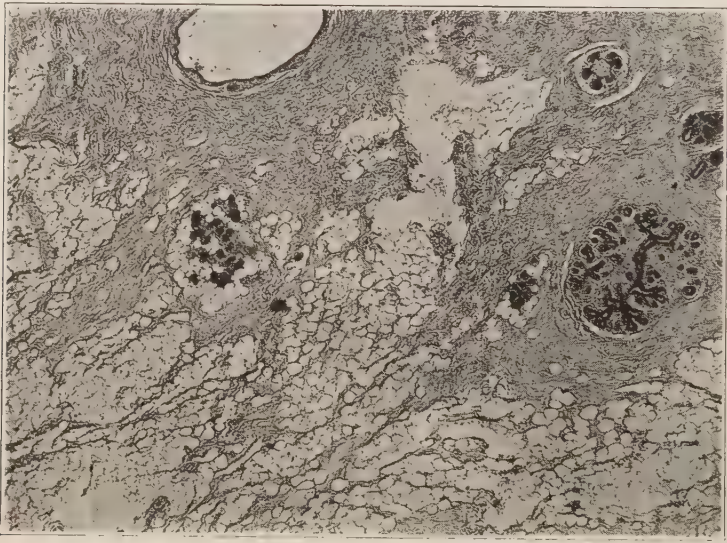
Fig. 18. — Specimen from the same breast as in Figure 17, showing, to the left of the center, fat deposited in the perilobular tissue. This is very rare in the human breast but it is the chief mode of assisting in the removal of the excessive parenchyma in the rat after lactation has ended.

the disappearance of the epithelial cells, the lobule loses a great deal of its nuclear appearance and comes to resemble more closely the classical lobule, except that the periductal tissue seems to be in excess, and usually irregularly distributed, loose and nuclear. As time goes on, the periductal tissue becomes more and more condensed or differentiated and the alveoli compressed. The latter grow smaller and smaller, and one by one disappear, as the whole lobule shrinks more and more. Eventually, the once large lobule is represented by a minute congeries of alveoli surrounded by a very small amount of, or perhaps by no distinctly recognizable, periductal tissue, and a mere vestige of

a lobule (vestigial lobule). In the course of time these also may disappear, and the only parenchyma to be found in the breast may be its ducts. In cases with complicating conditions, things may progress differently.

The simplest form of complication is conceived to result from the continuance of the function of secretion by some of the acini after the greater number have ceased, a greater and more disturbing complication than that which results from the retention of secretion in the ducts. This kind of interruption of involution may affect all of the acini of a lobule, but far more frequently only a few of them. When it occurs, the unaffected acini undergo the changes
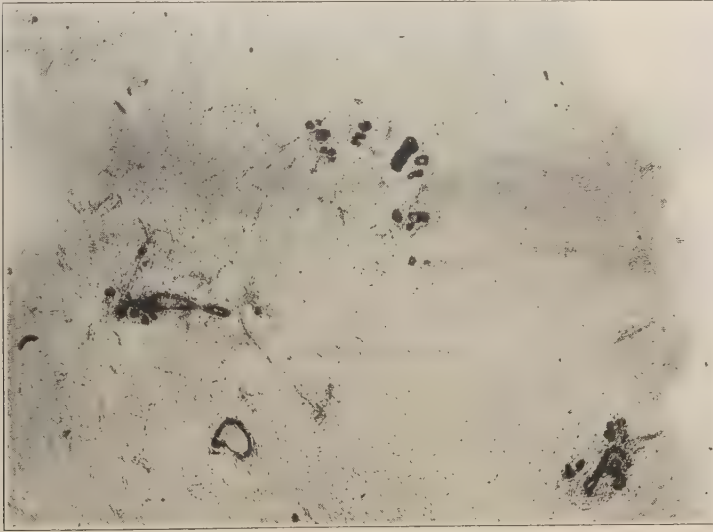
Fig. 19.—Necropsy specimen from the normal breast of J. H., white woman, aged 58, showing uncircumscribed vestigial lobules in the postclimacteric breast. The stroma of this breast was highly mucinoid and but slightly fatty. (From the Philadelphia General Hospital.)

already described, while the affected ones remain dilated and their cells unchanged. The subsequent events seem to depend upon the duration and permanence of the acinar dilatation. Beginning with cases in which the secretory function soon ceases, or the detained secretion escapes, it is found that the emptied acini, instead of retracting and contracting, now collapse, their opposed surfaces falling together, so that the formerly rounded spaces become fissures of crevices in the cellular area representing the lobule. In such cases, which by the way are rare, the whole lobular parenchyma seems sometimes to undergo disappearance by softening, beginning in the more centrally situated

portion, and extending peripherally, resolving itself into more or less unrecognizable débris, which when later removed leaves an irregular space.

But when the secretory function persists, or obstruction prevents the escape of secretion already within the acini, the undilated acini in the lobule follow the usual plan of involution, while those that are dilated remain unchanged as long as the secretion is present, or at least until the periductal increase, which seems to lead to, or assist in, the parenchymatous extinction, is completed, and one of the prime factors in involution has disappeared. The result is the frequent presence in lobules, otherwise well advanced in involution, of single or
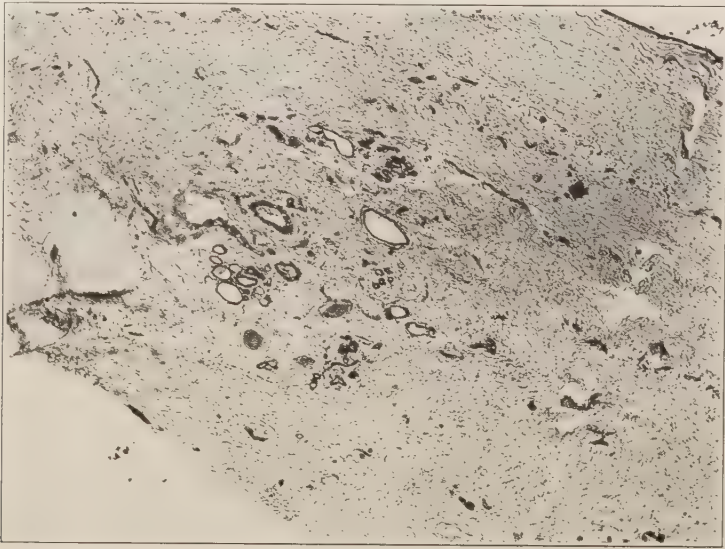
Fig. 20.—Necropsy specimen from normal breast of F. B., aged 62, white, widow, showing uncircumscribed vestigial lobules in the breast after the menopause. (From the Philadelphia General Hospital.)

multiple rounded spaces, usually appearing at the edges of the lobules in the beginning, but projecting from the edges as they grow smaller, and eventually becoming entirely separated from them, though still in approximation to them as their disappearance progresses. Though the acinar epithelium elsewhere disappears, and assumes in the alveoli, which represent its only surviving remnants, a crowded and indefinite arrangement, that lining these residual acini retains much its original character and appears as a single layer of distinctly cuboidal, or, even in some cases, almost columnar cells, possessed of considerable cytoplasm. Such structures are present in many sections of mammary glands, and are commonly looked upon as sections of ducts, or groups of ducts.

The occurrence of such acini, in varying degrees of moderate dilatation, among others naturally retracted and extinguished, causes a peculiar form of lobular disruption, that constitutes one of the most striking signs of past lactation. They may be described as uncircumscribed lobules.

The peculiar behavior of the periductal tissue and the relatively large quantity of it that appears at the time of involution lead to the conclusion that it plays an important part in the extinction of the epithelium. Appearing as a highly cellular and excessively nucleated tissue, it soon passes beyond the nucleated stage, and becomes fibrillar. Its quantity varies greatly in different cases, that is, in the breasts

Fig. 21.—Necropsy specimen from normal breast of C. R., aged 84, white, widow. There are no lobules, but their former position is indicated by epithelial lined fissures surrounded by condensed connective tissue formed by mixture of periductal and perilobular tissue. The relation of the interlobular tissue to this altered perilobular tissue is well shown. (From the Philadelphia General Hospital.)

of different persons, in the different breasts of the same person, in different parts of the same breast, and in different parts of the same lobule.

In what may be regarded as typical cases it is not strongly in evidence, and the typical textbook lobule results from comparative uniformity in its distribution; but from this it passes through every intermediate step to cases in which it is so excessive as to suggest beginning periductal fibroma. In some cases it presents a mucoid appearance, that is, its fibers seem to be separated widely by some

intermediate translucent substance, as in embryonal tissue. Under these conditions it becomes striking, giving the decadent lobule a great size and exaggerated importance. Like the epithelial elements of the parenchyma, however, it seems doomed to final extinction, and it is easy to determine the truth of this by the examination of a series of breasts of women that have passed the menopause, in not one of which are excesses of the periductal tissue to be found. In very rare cases fat cells penetrate into the periductal tissue.

Its final disappearance as an important structure seems to take place by contraction, by rearrangement and by confusion with the peri-lobular tissue. For a long time, it is a distinct entity surrounding the
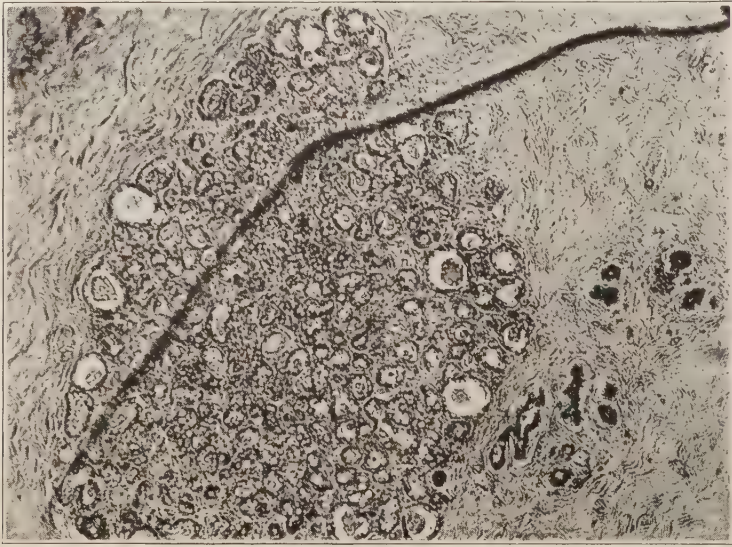
Fig. 22.—Necropsy specimen from breast of L. J., colored woman, aged 19, who died of hemorrhage from ruptured ectopic pregnancy in the third month of the second pregnancy. The section shows a new lobule developing to the left of an old one in advanced involution. (From the Philadelphia General Hospital.)

alveolar elements, sharply separating itself from the perilobular tissue and making a sharp boundary for the lobular structure. As the lobules, however, more and more completely disappear in the breasts of the aged, it becomes less distinct, blending more and more with the peri-lobular tissue, until it may be difficult to define. There are cases in which the breasts of old women contain small, regularly formed atypical parenchymatous structures that may be either rudimentary or vestigial structures.

In estimating the rapidity of involution, and noting the disappear-ance of the lobules after the menopause, allowance must be made for

certain circumstances that seem to play an important rôle in their extinction, namely, the age at which the last child was born, and the number of children the woman has had. Thus, accepting 47 as the average age at which the menopause occurs, some women have their last child but a year or two before, others as many as twenty-five years before. In the former case there will be large quantities of parenchyma to be got rid of, at the age when the greater part of it should already have disappeared, and when some exhaustion of the force of involution might be expected.

Occasional breasts contain large lobules years after the menopause, and in some cases small lobules as well as vestigial lobules can be found until old age. The facts as given above, however, apply to the average
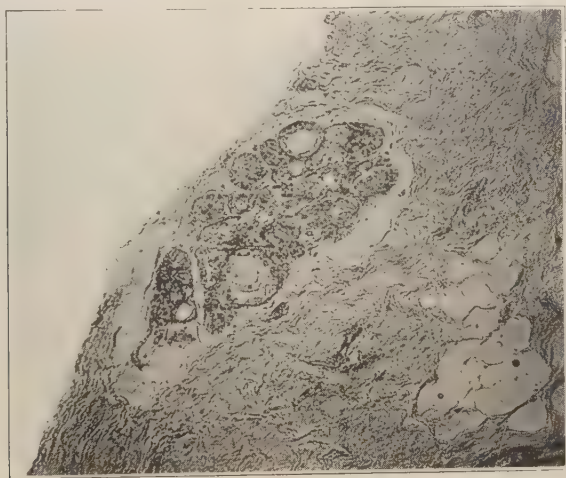
Fig. 23.—Necropsy specimen from normal breast of M. A., white woman, aged 87, married, showing a small lobule composed of residual lactation acini, with degenerated eosinophilic cytoplasm of the remaining epithelial cells. Many of the cells are without nuclei, and some have become fused into ill-defined masses. All of the remaining parenchymatous elements in the breast showed the usual staining quality. (From the Philadelphia General Hospital.)

case, and the conclusions are based upon the careful study of fifty-four breasts of women, more than 47 years of age.

Before dismissing the subject it is necessary to point out that the rapid growth and excessive development of the periductal tissue seem to be a function of youth, and that involution seems to progress much more rapidly at that time than in later life.

It is possible that with each successive lactation a new group of lobules evolves and declines. It is usually taught that the second, and later, lobular developments are through the resurrection of the alveoli that have previously entered upon the "resting state." This may need

confirmation. It is sometimes possible to see in the breasts of those that have died early in a second, or later, pregnancy the newly forming lobules, as well as the relics of the antecedent ones. In one such case the new acini were seen forming in close juxtaposition to an old lobule, but seemed to be quite independent of its structure.

It may be, therefore, that the lobule having once performed its function declines toward final extinction, new parenchyma for each lactation being formed, as the preceding parenchyma was, through budding from the ducts.

The most striking appearances observed in the course of mammary involution result from the survival of some of the lactation acini. These
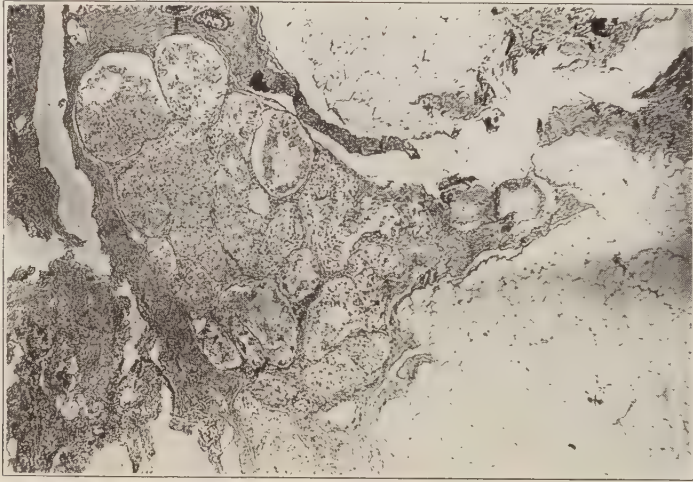
Fig. 24.—Necropsy specimen from normal breast of M. E., colored woman, aged 55, married, twice pregnant. The only lobule composed of residual lactation acini is shown in the illustration. It showed highly atrophic eosinophilic epithelial cells, with scarcely any intermediate or surrounding periductal tissue. There was scarcely any dilatation of the acini. All the other glandular tissue found in the section had followed the usual type of involution. (From the Philadelphia General Hospital.)

will be spoken of as residual lactation acini. They are of frequent occurrence, present a variety of appearances, and have been the subject of various and erroneous interpretation, the most important of which is the supposition that they are the beginning of tumor development.

RESIDUAL LACTATION ACINI

The residual lactation acini are undoubtedly known to all surgical pathologists and have attracted much attention, but few pathologists have busied themselves so much in endeavoring to determine what they

are, as in determining what they might do. It was in reality the latter question that was the starting point of the present investigation. But before it was possible to answer that question it was necessary to find out what they were. It seems, therefore, best to continue the consideration from that point of view.

They are well recognized entities in cases of cancer of the breast, and occur in such close relationship to the cancer nests as easily to have led to the supposition that they are its starting point. They are not infrequently pointed out as the precancerous condition—"precancerous stage of cancer." They are also frequently found in normal
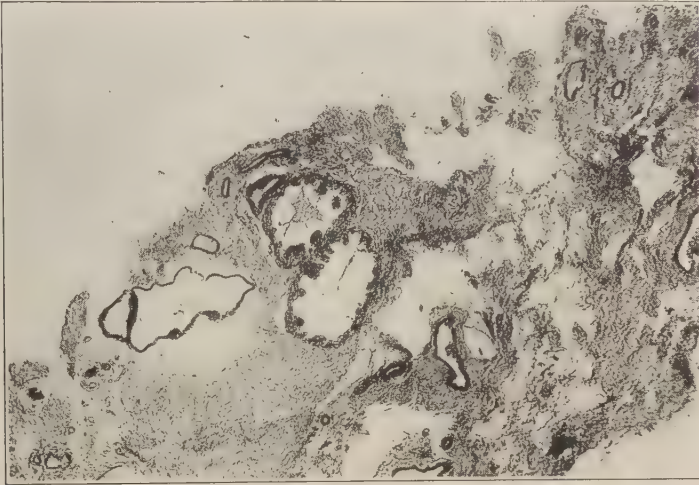
Fig. 25.—Necropsy specimen from normal breast of E. R., aged 72, white, married, mother of one daughter. Two minute cystic residual lactation acini, from the walls of which short rounded stumps of preexisting interacinar septums project. These consist of irregularly cuboidal or columnar epithelial cells, amalgamated into coalescent masses in some of the knobbed processes, and show markedly eosinophilic cytoplasm. The nuclei, when preserved, stain uniformly and intensely. (From the Philadelphia General Hospital.)

breasts, then suggesting other and different explanations, as, for example, Krompecher's theory that they are aberrant sweat glands included in the mammary structure. It seems as though all of these opinions are but the result of inadequate knowledge of the process of involution and the many different appearances to which it may give origin.

In the present research all of the appearances presented by normal breasts collected at necropsy have been carefully collected, arranged in a series that is supposed to express the whole sequence of events in involution, complicated as well as uncomplicated; and in this series,

these curious residual lactation acini have their regular place. It has already been pointed out that occasional acini, singly or in groups, sometimes fail to undergo involution at the regular time because of complicating circumstances. It next becomes necessary to determine what becomes of them.

When a single acinus is thus disturbed, it soon appears in a marginal position because of the disappearance of its fellows, and may even seem to be an entirely separate and independent entity of ductlike appearance; groups of acini meeting the same fate appear as approximate ducts, and may be passed by the microscopist without arousing interest. It seems possible that occasional structures of this kind may
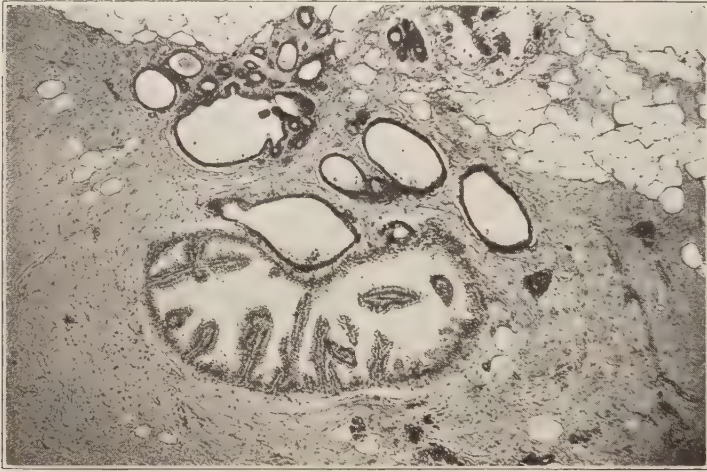
Fig. 26.—Necropsy specimen from normal breast of E. K., white woman, aged 59, married, no additional data. The specimen shows a group of residual lactation acini with marked projecting stumps of atrophic interacinar partitions. The epithelial cells lining the spaces and covering the stumps are columnar in shape and highly eosinophilic. They are distinctly atrophic, and confluence of approximated cells is frequent. (From the Philadelphia General Hospital.)

disappear, or if they were widely dilated, may contract, and substantially change their appearance, the lining epithelial cell layer being thrown into wrinkles, and the cells crowded and compressed so as to appear to be present in several layers, to be elongated, columnar and, in rare instances, of spindle shape. On the other hand, the space may undergo further dilatation through the addition of fluid contents, until a microcyst is formed. Under these circumstances the space becomes surrounded with flattened epithelium. They usually escape much attention, being supposed to be dilated ducts.

If instead of single acini, groups of them or considerable parts of the lobule become residual, a different appearance results. Atrophy, either as a manifestation of the general process of involution or from the pressure exerted by the dilated spaces, may cause the interacinar septums to disappear, and the neighboring spaces to coalesce into a larger space, either regular in shape if filled with fluid, or irregular if partly empty, and made peculiar and striking in appearance by the presence of relics of the former partitions that remain projecting from the margins in the form of stumps that may be simple and suggest folds or wrinkles, or complicated and suggest papillary excrescences. So long as the lining epithelial cells are not substantially altered, even these may be overlooked, or regarded as evidences of unimpor-

Fig. 27.—Necropsy specimen from normal breast of A. W., colored woman, aged 40. Nothing concerning the personal history of this patient could be found out. Her breasts, however, showed such quantities of parenchyma in advanced involution that there seemed to be no doubt of antecedent lactation. The irregularity of involution and the delay in the atrophy of a few acini of a lobule are well shown, as is also the thinned interacinar partitions, some of which seem to be rupturing. In this case the epithelial cells had not yet assumed the eosinophilic quality that comes with advanced atrophic change. (From the Philadelphia General Hospital.)

tant proliferation of benign character. But if, as so commonly happens, the cells take on a highly eosinophilic staining quality, the whole formation becomes so striking in appearance as to excite interest and give rise to speculation. Such spaces, lined with eosinophilic epithelial cells seem occasionally to retract, their crowded cells becoming compressed, assuming either a columnar or the spindle shape. The cells may also occur in several layers; the acini may continue to dilate, and the interspaces to attenuate until neighboring acini, of large size,

become separated by mere shreds of interacinar connective tissue, with epithelial cells on either side. These later attenuate to the point of rupture, when neighboring spaces coalesce with the formation of cysts. It makes no difference whether the rupture of the partitions comes early, while they are relatively thick, or later when they are thinned by distention; the end-result is the same. There is, in either case, the formation of a larger space into which the vestiges of the original partitions project as stumps, covered on both sides with the same eosinophilic epithelium that originally lined the acini. In a few cases the spaces collapse, their walls fall together, and there result slitlike spaces of elongated shape, like empty ducts.

More frequently, however, the spaces continuously dilate until they become cysts, varying in size from visibility to several centi-
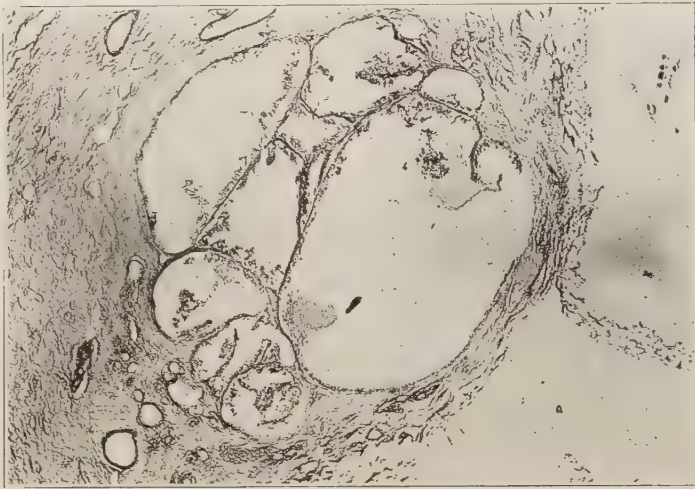
Fig. 28.—Necropsy specimen from normal breast of A. C., white woman, aged 55, married, showing a group of residual lactation acini. The partition walls are extremely attenuated and some have ruptured, leaving stumps projecting. Eosinophilia was just appearing in some of the cells in this area. (From the Philadelphia General Hospital.)

meters in diameter ("blue domed cysts" of Bloodgood), in the beginning lined with high columnar eosinophilic epithelium, sometimes in several layers, later with cuboidal cells, still later with flattened cells, and finally without distinct cells of any kind.

The varying appearances presented in different cases and at different times by the residual lactation acini, may be arranged serially as follows:

1. Single acini, or groups of acini that differ from their fellows in the same lobule, in that they escape involution and remain dilated.

2. Similar structural units, remaining at the edges or near the periphery of lobules well advanced in the process of involution. They are lined with single or multiple layers of epithelial cells like those of the acini in general, though sometimes the cells are more columnar in shape and more crowded.

3. Similar units, with all of the described qualities, occurring in the perilobular tissue, and seemingly apart from any lobules.

4. Groups of such units, the individual members of which are separated from one another by considerable intervals of fibrillar connective tissue.

5. Groups whose members are separated by narrow intervals, scarcely consisting of more than a double row of epithelial cells.
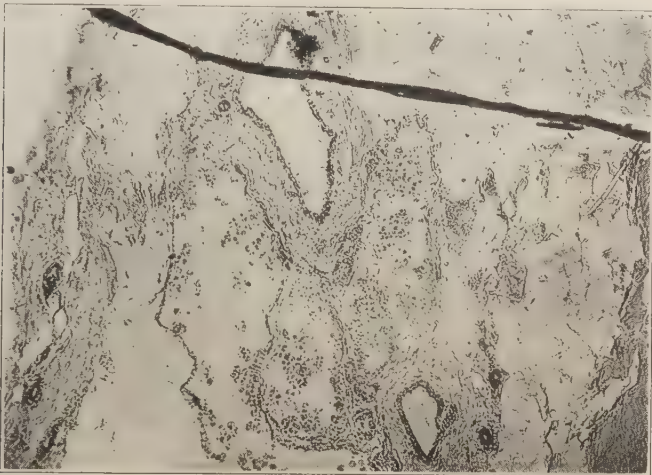
Fig. 29.—Necropsy specimen from normal breast of B. D., white woman, aged 75, married, showing three residual lactation acini very indistinctly, because the eosinophilic quality of the cells was so marked as to make it difficult to photograph their red bodies. The partitions are thin but have held, and there are no stumps. The spaces give the impression of partial collapse. (From the Philadelphia General Hospital.)

6. Groups in which the contraction of the space crowds the epithelial cells and causes them to encroach upon the lumen, with an appearance of proliferation.

7. Groups in which distention of the space results in the formation of microcysts, with various epithelial cell linings.

8. Groups in which the epithelial cells early acquire an eosinophilic staining quality, and a relatively large size. Such quality may characterize any of the groups previously mentioned.

9. Groups of any of the foregoing in which the atrophy of the intermediate partitions between the units causes them to coalesce.

10. Groups of such kind in which the stumps of the partitions remain projecting into the common space, covered with epithelium of the same quality as that which lines the spaces.

11. Cystic dilatation of such coalescent acinar spaces, with gradual obliteration of the projecting stumps of the original interacinar spaces.

12. Cysts that may be several centimeters in diameter, formed through the dilatation of single or coalescent acini of any of the forms mentioned.

13. Irregular crevices or spaces in the tissue of the breast that follow atrophy of the interacinar partitions and collapse of the acini.

Thus, the careful study of what is to be found in the normal breast in its various stages of involution, and the arrangement of the peculiar modifications of the process of involution in series, leads to

Fig. 30.—Necropsy specimen from normal breast of F. B., aged 68, white widow, showing several residual lactation acini; the larger with stumps of atrophied interacinar septums projecting from the upper side. The scanty epithelial lining was highly eosinophilic in quality and cells had frequently coalesced. (From the Philadelphia General Hospital.)

the inevitable conclusion that the "Schweiszdrüsen" of Krompecher, the "cyst-adenoma" of Schimmelbusch, the "senile parenchymatous hypertrophy" of Bloodgood, the "abnormal involution" of Warren, the "secondary epithelial hyperplasia" of McCarthy, etc., are no more than variations in the involutional process, in which residual lactation acini appear in various conditions of retrogressive change.

One of the first to call attention to the presence of the residual lactation acini, and to connect them with the process of involution, seems to have been Charles Creighton, in his book "Contributions to the

Physiology and Pathology of the Breast," published in 1878. He, however, made the error of supposing that they were abnormal, and, as others have ever since done, assumed that they were the starting point of malignant tumors.

Creighton saw the changes in the mammary gland of a bitch, and as it seemed to him to be a striking variation from the normal, concluded that it must be abnormal. Had he studied many, instead of a few, glands, he might have come to a different conclusion.

But this brings up the pertinent question of its normality or abnormality. The mammary glands that formed the material for this
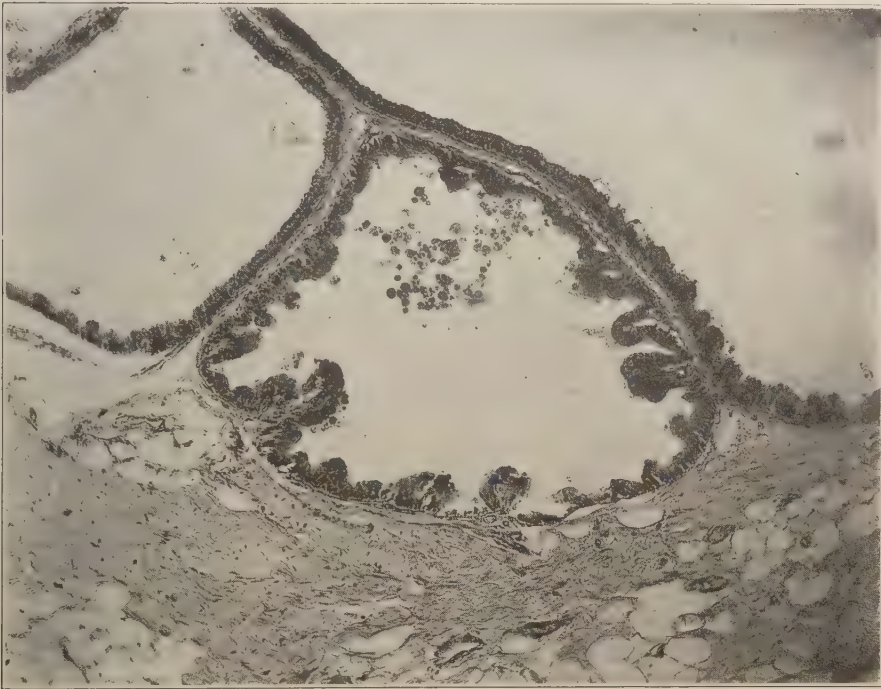
Fig. 31.—Surgical specimen from the breast of a married woman of whose personal history no data could be obtained, showing the smallest of a group of small cysts. The organ was supposed to be cancerous, but no disease was found. The irregular epithelial lining shows well, and the stumps of the former interacinar septums are numerous. All of the epithelium is highly eosinophilic; many of the cells are shapeless, and some have coalesced. The débris seems to be composed of eosinophilic cell remnants.

research were, as nearly as could be determined, normal; that is, they were taken at necropsy from organs seemingly normal, and from the bodies of those that had not complained of breast troubles during life. The authorities of the hospital from which most of the material was obtained do not permit the mutilation of bodies upon which

necropsies are performed, and are strict about the number and character of the incisions permitted, so the removal and examination of the entire breast was not possible. Fragments alone were obtained for examination, removed from the back of the breast exposed as the tissues were dissected from the chest wall. In most cases the amount of tissue was small, and selected without any definite purpose in view. A more thorough exploration might have afforded added opportunity of demonstrating the presence of the residual lactation acini. But of the material obtained in this somewhat haphazard fashion, twenty-three of the 150 mammary glands showed their presence—15.33
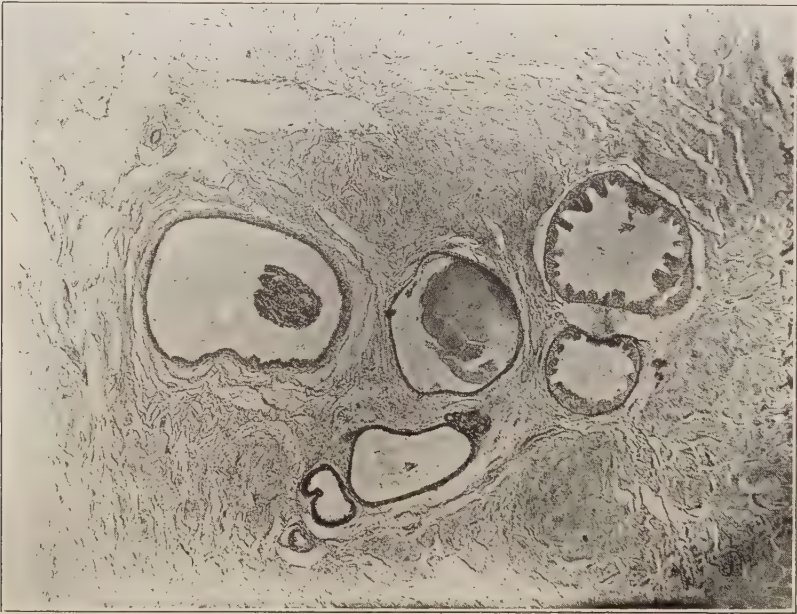
Fig. 32.—Necropsy specimen from normal breast of A. McL., aged 66, white, widow, with one child, showing a group of microcysts. Two of them, on the right, show interacinar stumps and have eosinophilic epithelium. (From the Philadelphia General Hospital.)

per cent. Is that to be regarded as abnormal that occurs in such a large number of cases?

But inasmuch as a number of the cases were inappropriate for the discovery of the residual lactation acini because the women from whom they were taken had never lactated, the percentage rises when it is based upon the cases in which it ought to appear. Among the 150 cases, there were ninety-two in which the women were known to have been married or to have had children, and of these the residual lactation acini occurred in twenty-three, or 25 per cent. Thus, it seems

that one fourth of the women whose breasts have been functionally active show this modification of involution, even though the examination of their breasts was superficially made. The average age of the women in whose breasts residual lactation acini were found was 59 years. The youngest was 33, the oldest 103 years.

But the final confirmation of the theory rests upon the demonstration of residual lactation acini in the breasts of women that have been pregnant, and their constant absence from the breasts of others. This requirement it is impossible to fulfil because of the impossibility of

Fig. 33.—Surgical specimen showing a group of cysts, distinctly visible to the naked eye, in relation to the involuted lobule from whose dilated elements they sprang. These cysts have smooth walls.

accurately determining who had and who had not been pregnant among women, some of whom may for a variety of reasons conceal or deny it.

The following plan seemed to be an appropriate means for reaching the truth as nearly as possible:

I. The determination of the percentages of married and single women among the cases of normal breasts secured at necropsy, in which the residual lactation acini were found. The results were: cases, 23: married, 23—100 per cent.; single, 0—0 per cent.

II. As the presence of residual lactation acini is one of the criteria for the diagnosis of the condition variously described as chronic cystic mastitis, abnormal involution, cyst-adenoma, etc., to assemble as many of these surgical cases as possible, and determine the percentages of married and single women among them.

The results were: McManes Laboratory of Pathology, University of Pennsylvania, 4 cases; Laboratory of Surgical Pathology, University of Pennsylvania, 26 cases; Laboratory of Gynaecological Pathology, University of Pennsylvania, 8 cases; Laboratory of Surgical Pathology, Medico-Chirurgical Hospital, Philadelphia, 13 cases; Laboratory of the Lankenau Hospital, Philadelphia, 15 cases, and Laboratory of the Presbyterian Hospital, Philadelphia, 1 case; total, 67 cases.
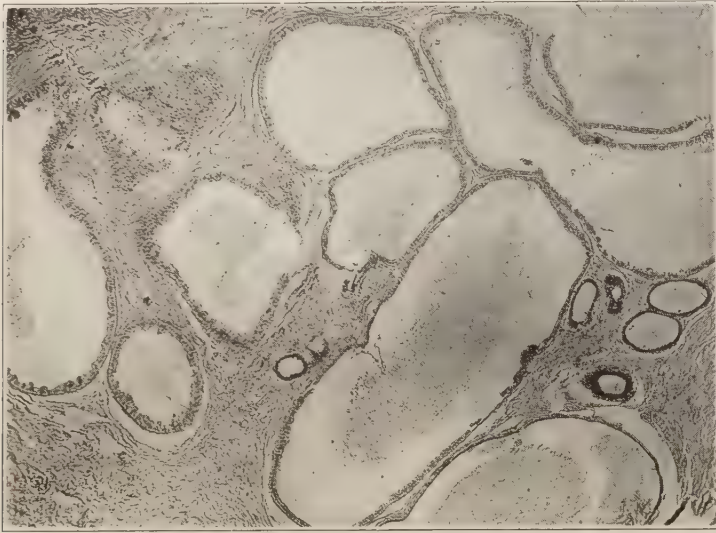
Fig. 34.—Surgically removed but normal breast of M. M., aged 32, white, one child. It shows a collection of microcysts, with smooth walls and cuboidal epithelial lining. The cells are, however, highly eosinophilic. (From the Philadelphia General Hospital.)

These were divided thus: cases, 67: married, 53—79.1 per cent., single, 8—11.94 per cent.; unknown, 6.

III. By collecting all of the cases of cancer of the breast, combined with the condition mentioned above, and determining the percentages of married and single women, there were: cases, 13: married, 12—92.3 per cent.; single, 1—7.7 per cent.

IV. By histologic examination of the breasts of the "single" and "unknown" cases to see what they show in the way of signs of antecedent pregnancy and lactation. Of such cases there were: "single," normal cases from necropsy, 0; benign surgical cases, 8; malignant surgical cases (cases with cancer), 1; "unknown", 6; total, 15.

In every one of these fifteen cases, there were appearances highly suggestive of postlactation involution. But, as local disturbances sometimes arouse the mammary tissue to develop large lobules like those of pregnancy—as in the surroundings of the encapsulated benign tissues studied with Bloodgood—it is not possible to be certain that these women were parous.

V. If residual lactation acini are of frequent occurrence in the mammary glands of women, and have the origin ascribed to them, they ought also to occur in the mammary glands of animals. That they do is a matter easy of demonstration. In two of the mammae of the first bitch subjected to examination, they were found in abundance, and in the most characteristic form, with the typical eosinophilic epithelial
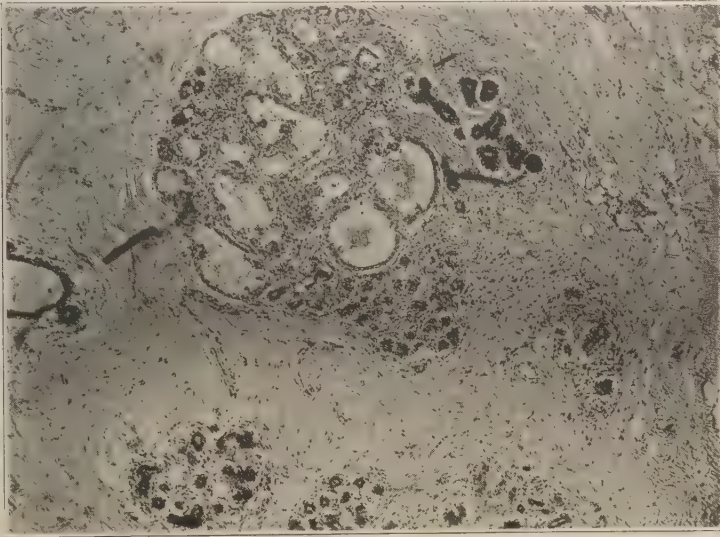
Fig. 35.—Necropsy specimen from normal breast of E. S., white woman, aged 44, married, showing early form of residual lactation acini in a breast, most of which shows ordinary and regular involution. Note that only the upper left part of the lobule is affected, and that the dilated acini are partly filled with amorphous matter. The pale appearance of the cells of the affected area as contrasted with the rest is due to their eosinophilic character. (From the Philadelphia General Hospital.)

cells. Indeed, in these glands, almost the entire gamut of the involution process could be followed. Analogous appearances were also found in the mammae of rats, though less typical, and lacking the eosinophilic character of the cells.

Attempts to ascribe a definite time limit to the involution of the mammary parenchyma after lactation have been without results. It seems to take place more rapidly in youth than later in life, so that the

age at which the individual became pregnant would affect it. Repeated pregnancies obscure the picture, through the introduction of new lobules, if they do not revive already existing ones. The time at which the involution process is begun must have great influence, because of the varying quantities of parenchyma to be dealt with. Thus, in cases of abortion or miscarriage, complete lactation hypertrophy does not occur, and involution begins in a gland only partly evolved. If the child is born dead, or if the mother refuses to nurse it, though the parenchyma be fully formed, it may not reach full secretory activity, and more easily undergoes involution than when it has secreted. If the secretion fails, the acini will perhaps be empty, and, the infant being artificially fed, the breast undergoes involution unimpeded by
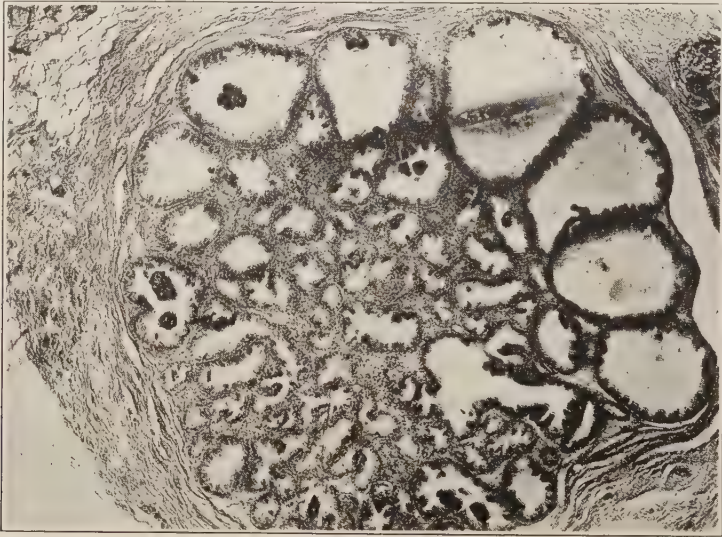
Fig. 36.—Specimen from normal breast, surgically removed, of A. B., aged 40, white, single, showing area of residual lactation acini which was found among normally appearing lobules of the textbook variety. The rupture of numerous interacinar partitions is shown. When such rupture occurs the cells are more highly eosinophilic than elsewhere; but the preservation of the area is too perfect to permit much eosinophilia. In various places the interacinar stumps are distinct.

accumulations of its own products. In any case the drainage of the mammary tissue may be unequal in different parts, and those that empty completely may atrophy more quickly than others in which some secretion is retained. So many factors thus combine to complicate the process in human beings that it is difficult to arrive at any conclusion, especially when to all these there must be added the inability to obtain precise information regarding the history of the patient.

But what is known is that in some cases, as that of the young woman of 19 years, to whom reference has already been made, most of the parenchyma had disappeared within a year after the birth of her baby, while in others, it remains for many years. In one case, that of a woman whose history is well known, the second child was born when she was about 27. At about 43 a breast was removed for "abnormal involution with suspicion of cancer." In it a tiny scirrhous carcinoma was found, entirely too small to have been recognized clinically, and all stages of mammary involution were found, among them a few lobules that still showed unchanged lactation hypertrophy resembling that seen in the fully acting breast, sixteen years after lactation. Between them and advanced involution of the lobules
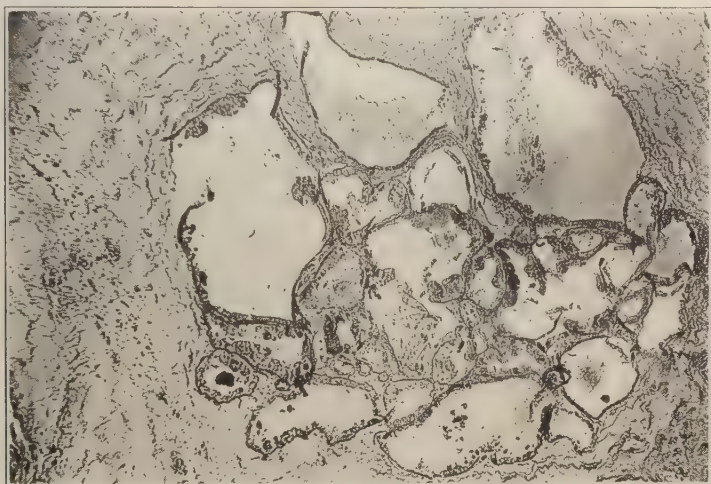
Fig. 37.—Necropsy specimen from normal breast of E. H., aged 60, white, married, one child. This beautiful area of residual lactation acini was somewhat injured in preparation, and was too highly eosinophilic to photograph well. It shows all stages from fairly well preserved acini to cystically dilated spaces without epithelial linings. Some of the spaces, such as that at the lower left, show interacinar stumps covered with highly eosinophilic cells. (From the Philadelphia General Hospital.)

there was every intermediate stage. What caused these lobules to remain unchanged throughout all those sixteen years could not be determined.

Seeing that a few or many of the mammary lobules may thus remain exempt from involution for so long a period, and that in many cases involution is very slow, it is not surprising that through delay in the involution of occasional units of the mammary structure the residual lactation acini may appear. Nor, having appeared, ought it be regarded as remarkable that they may persist.

But with the lapse of time they are likely to undergo certain changes. One of the earliest and most striking of these is the occurrence of the eosinophilic quality of the cytoplasm of the cells. In some cases this seems to make its appearance early; in others, late. Naturally, this is only a deduction, not a demonstrated fact, and is based upon the observation that it may occur in acini situated in the midst of lobules in an early stage of involution, at other times in groups of acini whose surroundings show them to be old, and in aged women.

In many cases, accumulated products of degeneration may be observed in the spaces formed by the coalescence of closely approximated acini, evidently composed of the detritus of the desquamated and disintegrated epithelial cells set free by the wasting and rupture
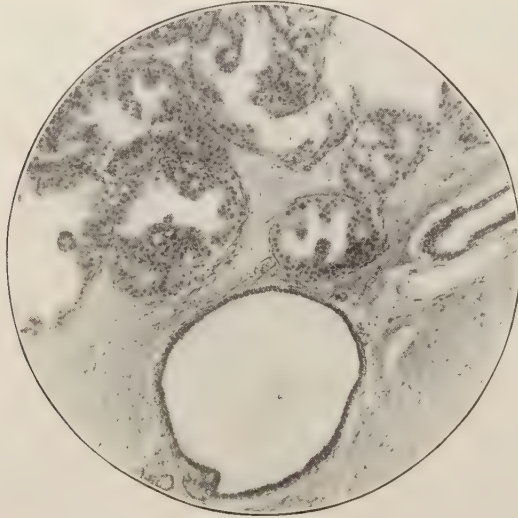
Fig. 38.—Specimen from a woman's breast, surgically removed and suspected of being carcinomatous. No other data available. No tumor of any kind was present, but several areas of residual lactation acini were found, one of which is shown in the illustration. The atrophy of the interacinar partitions is marked, and the eosinophilic quality of the epithelial cells well developed. The area shown in the illustration shows unruptured partitions, stumps of ruptured partitions, and amalgamated masses of cells.

of the interacinar partitions. The residual lactation acini differ greatly, however, in this respect. Many are empty, some contain a little, some are nearly filled with matter of varying quality, some like jelly, some granular, and some composed of pellets of amorphous matter, which in one case was found to have calcified, with the formation of laminated chalcospheres. Some of these accumulations may be as old as the acini themselves, and may have been the source of the obstruction to which the retardation of involution has been ascribed; but others are undoubt-

edly relatively recent. It seems, moreover, that to their presence may be referred the subsequent distention of the acini with the formation of cysts that seem to be of frequent occurrence. In regard to these it is not assumed that they act only or even chiefly as sources of obstruction, but as material whose transformation is accompanied by the formation of chemical products whose affinity for water leads to its accumulation with dilatation of the spaces. It is with the development of cysts of large size or considerable number that such cases become known to the surgeon from whom the patients seek advice, and by whom they are commonly operated on.
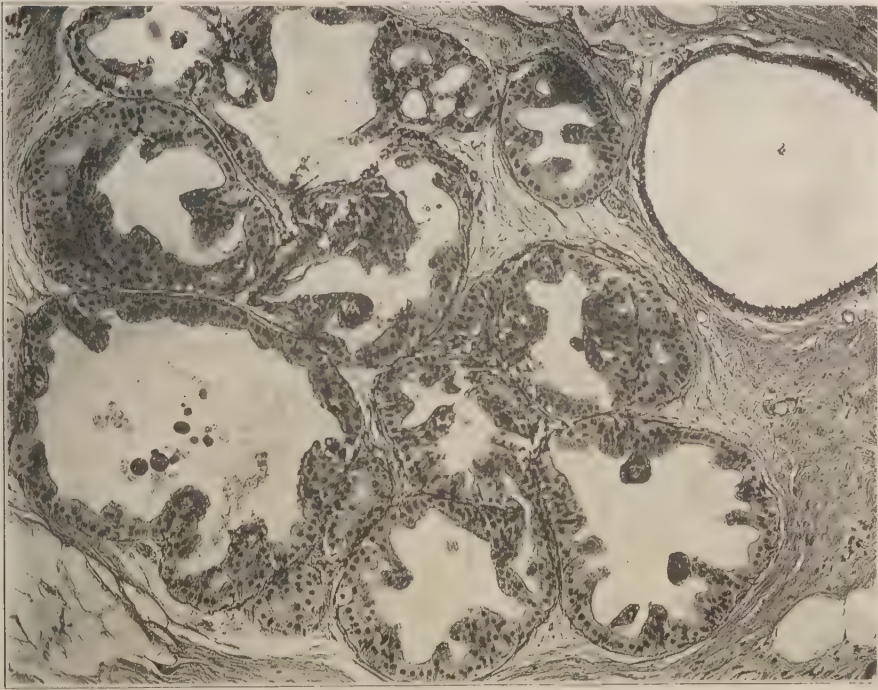
Fig. 39.—Specimen showing an area of residual lactation acini in a breast surgically removed for suspected cancer. No data concerning the patient was available. There was no tumor, and no other disease. The group of spaces is highly characteristic. Numerous acini are not much changed; others are united as the result of atrophy of the interacinar septums; relics of septums project in many places as stumps, some of which are reduced to budlike masses of amalgamated eosinophilic epithelial cells.

Since the term chronic cystic mastitis has been adopted by Bloodgood in his recent paper, it will be adopted here. Chronic cystic mastitis, though described in the textbooks, and elaborately discussed in many journal articles, is in reality a vague disturbance. The age at which it usually makes its appearance corresponds fairly well with the

child bearing period. It is clinically characterized by vague discomfort in one or both breasts, which when examined are found to be tender and to contain one or several ill-defined indurations, or "lumps," which sometimes confuse the surgeon by seeming to be present at certain times and absent at others.

It is pathologically characterized by cysts, occurring singly or in groups, surrounded by condensed stroma, in which mammary tissue in various quantity and different conditions is present. One of its striking, but not invariable, characteristics is the presence of parenchymatous structures, like exaggerated acini, or ducts, lined with more or less distinct columnar epithelium, from the walls of which simple or

Fig. 40.—Necropsy specimen of normal breast of T. S., aged 40, colored, widow, said not to have had children, a statement which the histologic structure of the breast makes very doubtful. The illustration shows one of the groups of spaces looked upon as residual lactation acini. It is, however, in an advanced state of atrophy with destructive transformation of nearly all of the cells. Projecting stumps with eosinophilic coalescent cells may still be seen in the space at the right edge. (From the Philadelphia General Hospital.)

dendritic projections extend into the lumina. Such lobules as appear in the examined tissue commonly present inequality of the periductal tissue.

Bloodgood's [1] article is one of the most masterly and comprehensive articles that have appeared on the subject, and is based on the macroscopic and microscopic examination of 350 cases—an overwhelming

1. Bloodgood, J. C.: The Pathology of Chronic Cystic Mastitis of the Female Breast, Arch. Surg. **3**:445 (Nov.) 1921.

volume of material, well studied, and well analyzed. If, however, he had not fallen into one of the most frequent errors to be avoided in pathologic work, that of comparing the cases with one another, instead of with the normal breast, the article would probably have been written in some other form, and the cumbersome nomenclature with which it terminates omitted.

Now when the findings in chronic cystic mastitis are carefully analyzed, and compared with the findings in the normal breast, they resolve themselves into very little, apart from the presence of the cysts. Taking first the condition of the stroma, it will be recalled that one of
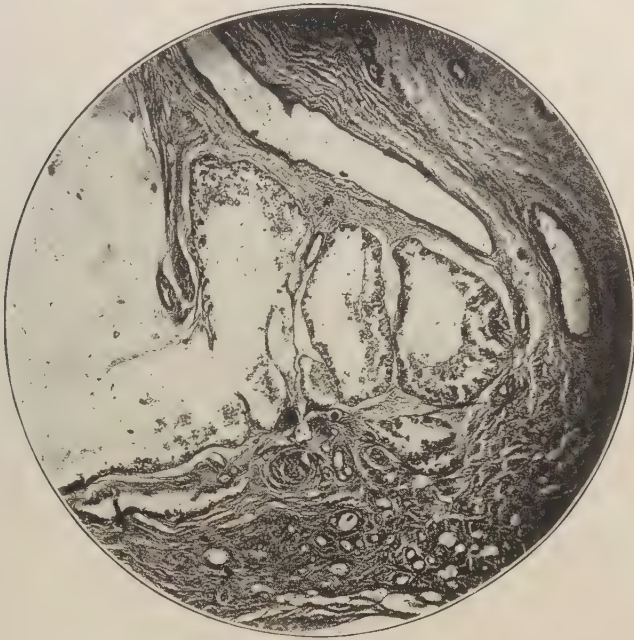
Fig. 41.—Section of a surgically removed breast, showing residual lactation acini similar to those seen in Figure 40.

the first observations made in the present research was that unless there was present some distinctive disturbance, such as round-cell infiltration, hemorrhage or calcification, nothing could be learned from its study because of the extreme variability of its normal structure. The presence of a growing cyst, pushing aside the fibrous tissue and causing atrophy of the adipose tissue, may give the stroma unusual density by condensation, but that is not chronic inflammation. The illustrations in Bloodgood's article show no disturbances that cause the stroma to differ from that seen in the normal breast.

When the periductal tissue is prominent, and especially when it lacks uniformity of distribution in the lobules, the condition is referred

to by Bloodgood as chronic cystic mastitis, but that is the condition of the same tissue in nearly all of the lobules of the normal breast. Nothing is shown as a pathologic change in this tissue that is not perfectly paralleled in the normal breasts that form the basis of the present research.

It must, therefore, be the parenchyma to which one is compelled to look for the specific changes. And here firm ground seems at first to have been reached, for there are many illustrations bearing the legend "papillary cyst-adenoma."

That designation for residual lactation acini has so frequently been dwelt on—not exactly that, but "cyst-adenoma"—that it immediately demands careful study of the illustrations to see how what is repre-
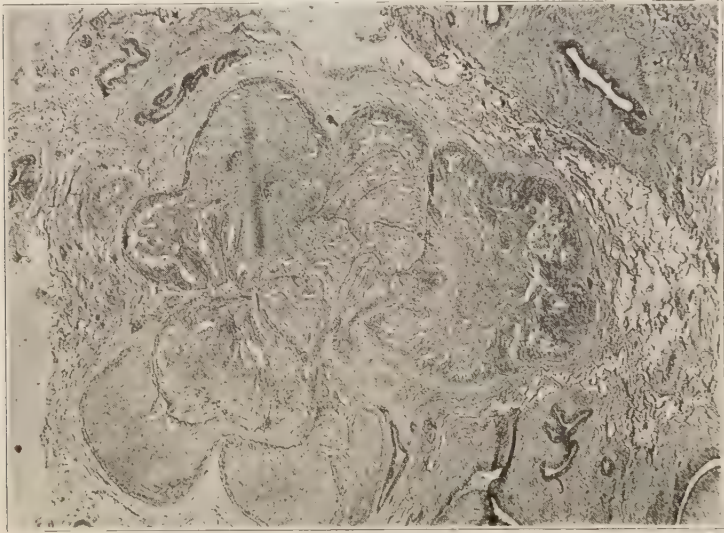
Fig. 42.—Necropsy specimen from normal breast of R. R., white woman, aged 54, married, showing a large lobule of residual lactation acini in which there has been very little atrophic change. The irregular slits in the parenchyma seem to be originally dilated spaces that have collapsed. The epithelial cells everywhere are in a fair state of preservation but are very pale, with pale vesicular nuclei, and slightly eosinophilic clear cytoplasm. The general appearance is like that seen in many cases shortly after lactation, except for the altered staining quality. (From the Philadelphia General Hospital.)

sented may differ from what has been the main subject of the present research. Comparison shows that there is no difference; they are the same. One is, therefore, compelled to question whether there is really anything to be found in these cases, except the cysts, that may not be present in the normal breast in some stage of its involution, with the inevitable discovery that there is not.

Chronic cystic mastitis, therefore, seems to resolve itself into no more than the occurrence in the breast of cysts of larger than usual size after postlactation involution, the other associated disturbances being no more than errors of interpretation based on inadequate familiarity with the details of the involution process.

It seems, therefore, that there being no mastitis in these cases, there can be no chronic cystic mastitis, and all that occurs is the presence of cysts of a size larger than that reached in the course of involution. But one matter of serious import is to be considered, and that is the emphasis laid on "adenoma," "cyst-adenoma" and above all on "papillary cyst adenoma" in Bloodgood's paper.

Fig. 43.—Necropsy specimen from normal breast of E. F., aged 56, white, widow, showing area of residual lactation acini in which the atrophic changes are further progressed than in Figure 42. The rounded space on the left still shows the skeleton of its acinar structure, while the irregular one on the right leaves one in doubt as to its nature. It might be either a completely transformed lobule or a duct filled with débris, such as must eventually result from further degeneration in the other. Scarcely any cells are recognizable except by their form and position, and all are eosinophilic. (From the Philadelphia General Hospital.)

The employment of these terms for the explanation of what could not be satisfactorily accounted for, namely, the dilated acini with their eosinophilic epithelium, and occasional mural papillary projections, termed, in this article, residual lactation acini, was first introduced by Schimmelbusch.

It is probable that Schimmelbusch had just as inadequate information on the manifold appearances presented by the breast in involution as any other pathologist, and that he, therefore, made a mistake. But it is a pity that it should be perpetuated by continued application to appearances common to a large number of the mammary glands of human beings and animals during mammary involution.

Bloodgood goes farther and seems entirely to disregard the fact that the mammary glands of women that have recently lactated contain large lobules, and in his illustrations he applies the term "nonencapsulated adenoma" to nearly all of the normal mammary parenchyma that appears in his sections. Thus the reader is left with the impression that the mammary gland is peculiar in that it may be the seat of "encap-
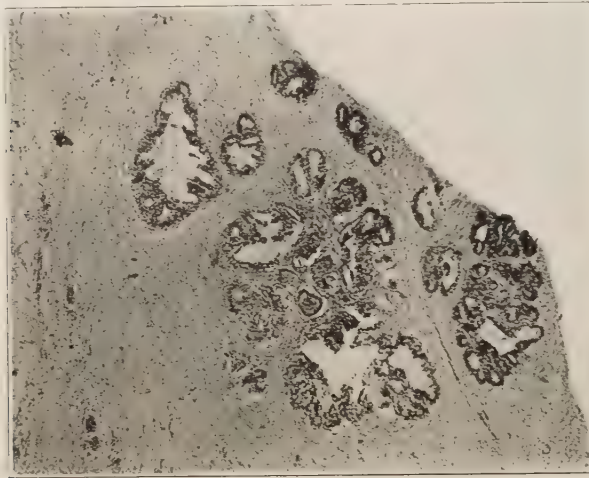
Fig. 44.—Necropsy specimen from normal breast of J. F., aged 75, white, widow, nine times pregnant. The residual lactation acini in this case are less distinct and less regular than those that have preceded it, and the cells lack the eosinophilic quality. The shape and general arrangement of the structure, however, leave one in little doubt as to its origin. (From the Philadelphia General Hospital.)

sulated" and "nonencapsulated" adenomas, the latter of which in no way differ in appearance from the normal mammary tissue, and of an uncircumscribed tumor, the "cyst-adenoma" which diffuses itself throughout the breast, or occurs at multiple foci.

Schimmelbusch's "cyst-adenoma" is a misinterpretation. It ascribes to the decadent residual lactation acini an importance of which they are unworthy, and leads to the belief that they are vital growing things, when the evidence is strikingly in favor of their being precisely the opposite.

From the examination of some single section, in which a group of the residual lactation acini are well preserved and provided, as sometimes happens with several rows of epithelial cells, or in which the collapse of the decadent acini causes crowding of the cells at particular points, it may sometimes be suggested that the appearances are proliferative; but after many cases have been studied, one becomes overwhelmed with the evidence to the contrary, manifested by the eosinophilic cytoplasm, the presence of anuclear cell remnants among the still living cells, the frequent desquamation of the cells without their regeneration, the contraction and condensation of many of the groups of acini, the necrotic residuum of amorphous matter that collects in the older lesions, and the general inactivity of the cells, and other fea-
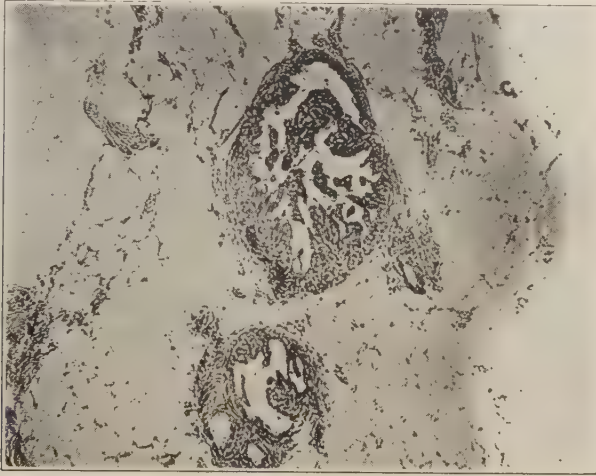
Fig. 45.—Necropsy specimen from normal breast of H. J., aged 103, widow, showing vestiges of residual lactation acini of great age, but still with enough of the remaining skeleton of the original lobule to explain their source. The cells were so atrophic as scarcely to be recognizable, and their remains were eosinophilic. Except for these few vestiges the lobular parenchyma of the gland had virtually disappeared. (From the Philadelphia General Hospital.)

tures not easy to describe. Beyond all this, there is the absence of any evidence, in spite of the study of many cases, to show that the formations ever do anything or develop into anything.

It is impossible, however, to neglect the papillary processes whose presence has excited so much interest and has led to the cases in which they occur being called "papillary cyst-adenoma." They certainly are peculiar and striking formations; but they, like so many others seen in connection with involution, have certain qualities by which their nature and origin are betrayed. As a rule they are few in number, simple in structure, do not interfere with one another, and not infrequently stand

opposite one another. These features are in marked contrast to other papillary excrescences—as, for example, those found in the cysts of the kidney and thyroid, where the number is usually large, the structure complexly branched, and the different formations crowded together so as to interdigitate.

The decadent quality of the eosinophilic protoplasm of the epithelial cells covering the processes, the adhesiveness that causes adjacent cells to coalesce, and the occasional occurrence of considerable masses of still separated ghosts of cells without nuclei, have already been referred to as far more indicative of retrogression than of vegetation. But the slightest effort of the imagination is sufficient to enable the broken
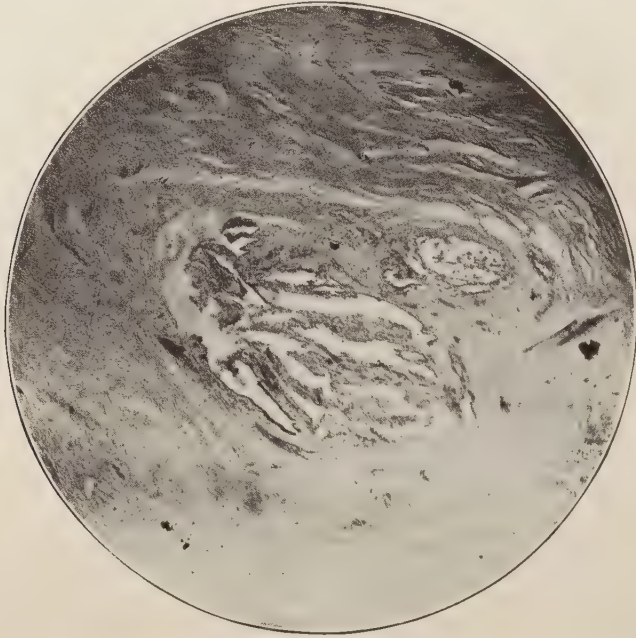
Fig. 46.—Specimen from a married woman, no history. In this lobule the epithelial cells have all disappeared, though the interacinar framework partly remains—a rare circumstance.

partitions to be reconstructed into the interacinar reticular framework, and the cystic space into an involuting lobule. There seems, therefore, to be good reason for abandoning the idea that in these residual lactation acini the first stages of tumor formation are to be seen, as well as the consequent fear that they may terminate in something malignant.

This now introduces the remaining question connected with the residual lactation acini, namely, the relation they may bear to cancer. The thought that they may originate cancer is widespread, and its origin not far to seek. The circumstance most feared in every dis-

turbance of the breast is "malignancy," and as its occurrence is very mysterious, and cannot be explained at present, the custom has been to examine every breast offered for study for such structural alterations and irregularities as might lead to it. Naturally, such striking objects as the residual lactation acini could not be overlooked, and there being no ready explanation of their meaning, they were gladly seized on as the probable starting point of tumor growth. In support of this view, the frequent concurrence of cancer with residual lactation acini was dwelt on. The cancer nests were shown to be in close juxtaposition to the formations of suspicious nature that were not understood, and it seemed as though the one might have developed through trans-
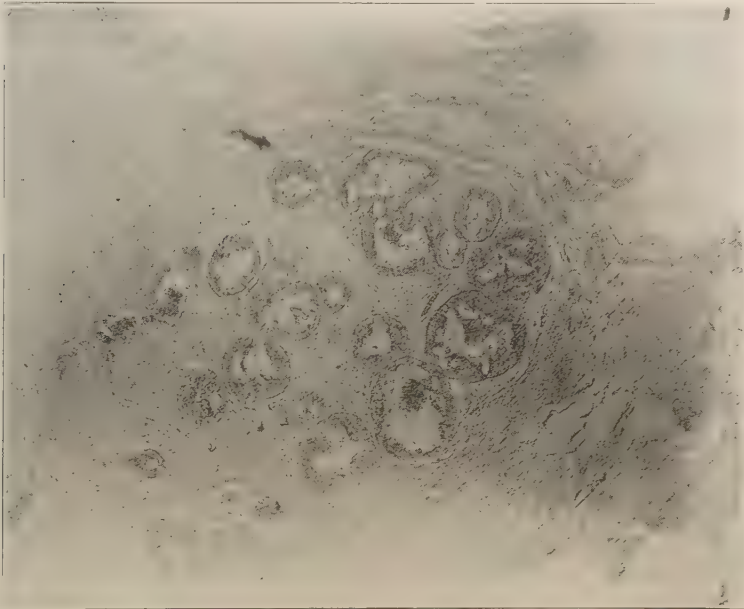
Fig. 47.—Necropsy specimen from normal breast of J. C., aged 75, white, widow. This patient was a hemiplegic with a leg ulcer, and was in the Philadelphia General Hospital for a long time. She was so frequently transferred from ward to ward that there are many "charts," but the one with her personal history could not be found. In the lobule shown, the unusual increase in the periductal tissue interfered with the union of many of the residual lactation acini. (From the Philadelphia General Hospital.)

formation of the other. Cancer cells frequently appear in the acinar spaces among their own peculiar epithelium, and many have supposed that they were able to find the transition steps between the one and the other.

The almost universally accepted theory of mammary cancer, of the present day, teaches that the cancer cells arise through metamorphosis

of the mammary cells themselves—that they are but the lawless descendants of those cells. This may be true, but it is at present only a theory, never having been proved. No one has ever seen the beginning of cancer. But once a theory meets with acceptance, it becomes a fact to the complacent mind. It is more easy to accept it than to combat it, and if it seems satisfactorily to explain the condition, why upset it?

So firmly is the theory rooted in the minds of pathologists of the present day that it is by no means unusual for a microscopist, examining a section of a cancer to select a microscopic field, and to demonstrate
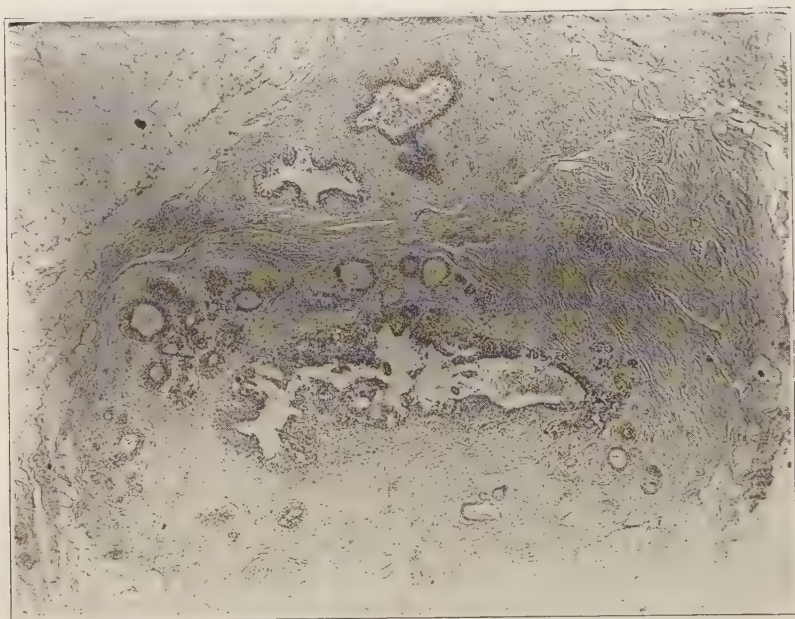
Fig. 48.—Necropsy specimen from normal breast of M. C., aged 51, white, married twice, had three children and two miscarriages. The menopause had occurred five years previously; her husband had died three years previously. As in Figure 47, the arrangement of the periductal tissue has modified the process of involution, and the destruction of the interacinar septums has resulted in the formation of an irregularly elongated space the margins of which, degenerated eosinophilic cells, and collections of cellular and amorphous débris betray its origin. (From the Philadelphia General Hospital.)

in it the primary rupture of the basement membrane of some glandular unit, from which the cells are escaping and beginning their lawless invasion. A moment's reflection ought to make him realize that such a demonstration necessarily implies that cancers have continuous and successive beginnings, for which there is no authority, since examinations by serial sections have repeatedly shown the entire cancer mass, with all of its extensions and prolongations, to be continuous.

In infiltrating cancer of the mammary gland it is really more reasonable to suppose that the cancer cells lawlessly and invasively penetrating the tissues are finding their way into the acini, than that the acinar cells are escaping to form the cancer. If the theory of "cystadenoma" is abandoned, and that of residual lactation acini adopted, the relation of the lesions to cancer can be examined without prejudice, and to advantage; for under these circumstances it will probably occur to the student that as most women become pregnant, and later nurse their offspring, the breasts of most women when examined microscopically must show parenchyma in some stage of involution, and as

Fig. 49.—Necropsy specimen from normal breast of A. G., aged 40, colored, widow, showing residual lactation acini surrounded by rinds of combined periductal and perilobular tissue similar to that shown in Figure 21. The atrophy of the parenchyma is so complete that the origin of the peculiar spaces might remain inexplicable without the study of the series of cases by which it is preceded. All of the cells are in an advanced state of degeneration. There is no proliferation. The degeneration of the cells and partitions has led to the formation of transformation products of rounded amorphous, more or less hyaline, appearance in the spaces. (From the Philadelphia General Hospital.)

residual lactation acini are of frequent occurrence in consequence of lactation hypertrophy, at least one fourth of the breasts may contain them. It, therefore, ceases to be a matter of concern or surprise that a breast examined for malignant disease shall contain residual lactation acini, with or without cancer. The frequency with which each occurs determines that they must frequently coexist.

But it has been argued that the relation of the cancer to the residual
lactation acini is too close to be accidental; it must be incidental.
There are many more cancer cells in those spaces than elsewhere, and
metamorphosis of the lining epithelium into cancer cells can be fol-
lowed. The same thing has been argued with respect to the acini, the
alveoli and the ducts of the mamma itself. In the absence of the
residual lactation acini, the origin of the neoplasm is traced to the
normal structures; in their presence, to the supposedly abnormal ones.
The logical outcome of this reasoning seems to be that the residual
lactation acini are no more likely to be the starting point of the malig-
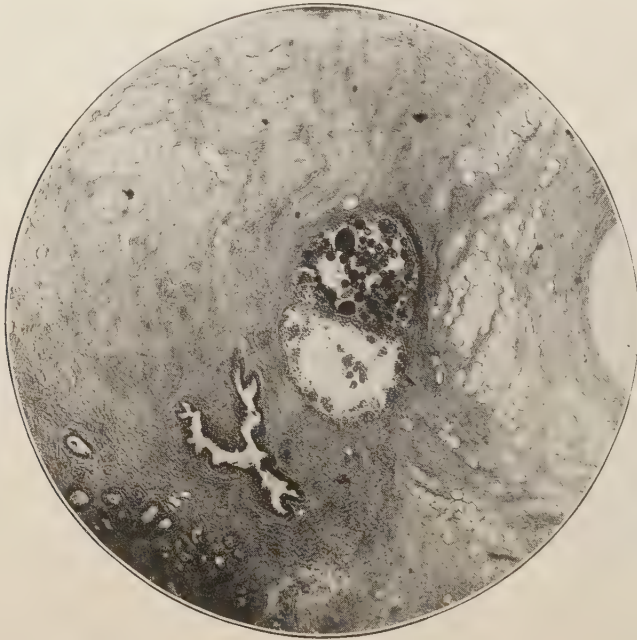
Fig. 50. — These residual lactation acini, discovered in a breast removed
for chronic cystic mastitis, show what may be looked upon as a possibly
later and final stage of what was shown in Figure 49. The parenchyma
having reached the stage of complete degeneration, the hyaline products have
calcified, with the formation of numerous small calcospherites which are
enclosed in a relatively clean walled pocket.

nant growth than the rest of the parenchyma, when, of course, they
lose their significance and importance. They may, however, effect a
close relationship between the growth of the cancer and the parenchyma
of the gland in that they provide spaces into which the cancer easily
infiltrates. Their decadent tissue may yield more readily to the invasion
than the more normal structures, and the spaces they form may afford
easy opportunity for the accumulation of cancer cells which mix with
the preexisting cells before extinguishing and replacing them.

It seems, from all this, that the conclusion that the irregularities of involution, including the residual lactation acini, have nothing to do with the origin of cancer is justified. The suspicion arose through misunderstanding and misinterpretation of the normal process. Very pertinent in this connection is the closing paragraph of Bloodgood's paper: "When good pathologists disagree as to malignancy, the patient lives; when there is agreement, there is always a large percentage of deaths." It is not difficult to account for this state of affairs. All of the good pathologists know cancer when they see it, but few of them
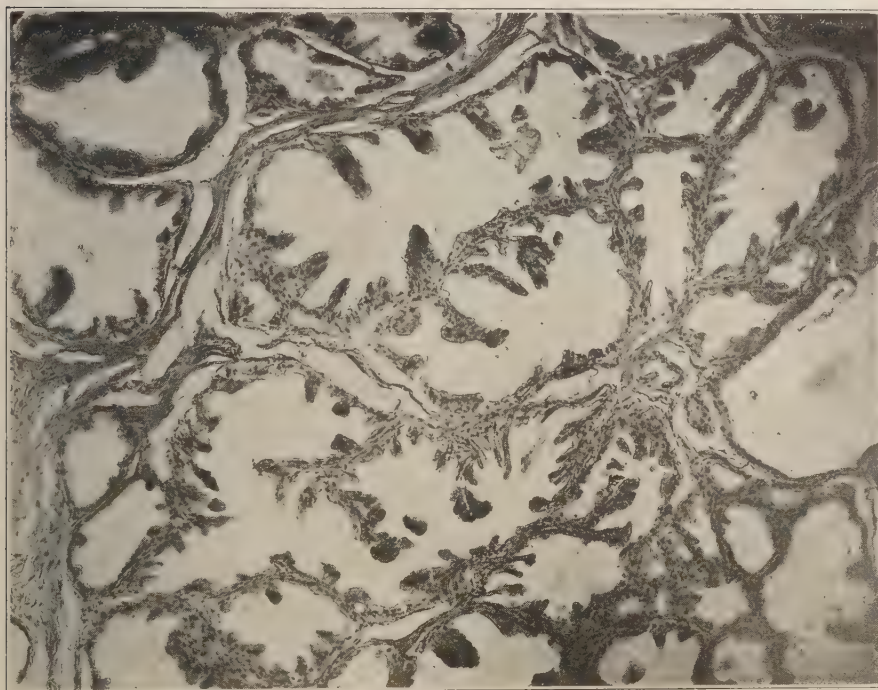
Fig. 51.—This breast was surgically removed and in it a very small scirrhous carcinoma was found. The patient had lactated twice, the second time sixteen years before the operation. All the modifications of involution were found, including the area of full lactation hypertrophy shown in the illustration, with no other change than eosinophilia of the atrophic epithelial cells, some of which had coalesced. The stumps of interacinar septums are numerous and striking.

are sufficiently acquainted with the conditions obtaining in the normal involution of the breast to be sure that such of its peculiarities as they see for the first time are not abnormal and indicative of a malignant change. Thus they fully agree with respect to the former, and disagree about the latter.

THE CYSTS OF THE BREAST

Cysts are like tumors in that after they attain a certain size it is no longer possible to determine from exactly what structures they arose. In the present connection it is unnecessary to consider any kinds other than those that arise through disturbance of the parenchyma of the breast. Such are extremely common and there seems to be very little objection to the general statement that they arise from very small beginnings.
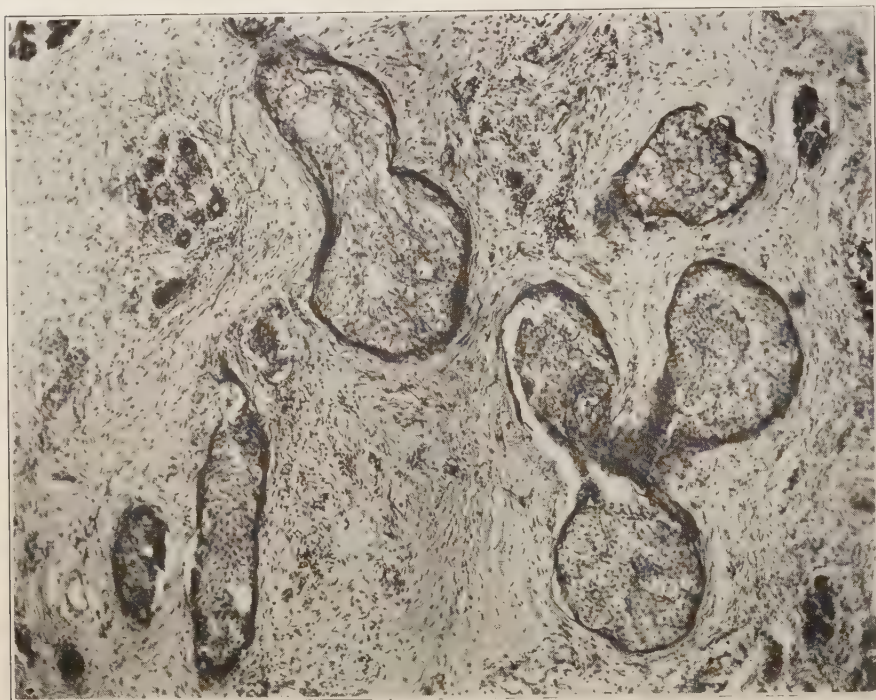
Fig. 52.—The area shown in the illustration, from the same breast as that shown in Figure 51, was far away from the cancer, and shows involution of several lobules, the atrophy of the interacinar partitions and slight transformation of the epithelial cells—"blasse-epithelzellen" giving the impression of dilated ducts filled with cells. The explanation of the cellular structure will become evident upon examination of the following illustrations of the same field under a higher magnification.

The examination of the material embraced in the present research suggests that there are only two sources from which they may originate, the ducts and the residual lactation acini.

In forty-nine of the 150 cases studied, the sections showed more or less rounded openings, visible to the naked eye, which microscopic examination proved to be epithelial lined spaces, for the most part

recognizable as ducts, but some of which were the residual lactation acini. In most cases they appeared empty; but some were filled with jelly. In all cases it seemed that distention was present or had been present. These were microcysts, and as such the larger cysts probably begin.

Two of the sections were from virgins (women that had not borne children), all the others were from parous women. In only two cases were there cysts having a diameter of more than 0.5 cm. This does not signify that this is the proportion of the larger cysts among normal
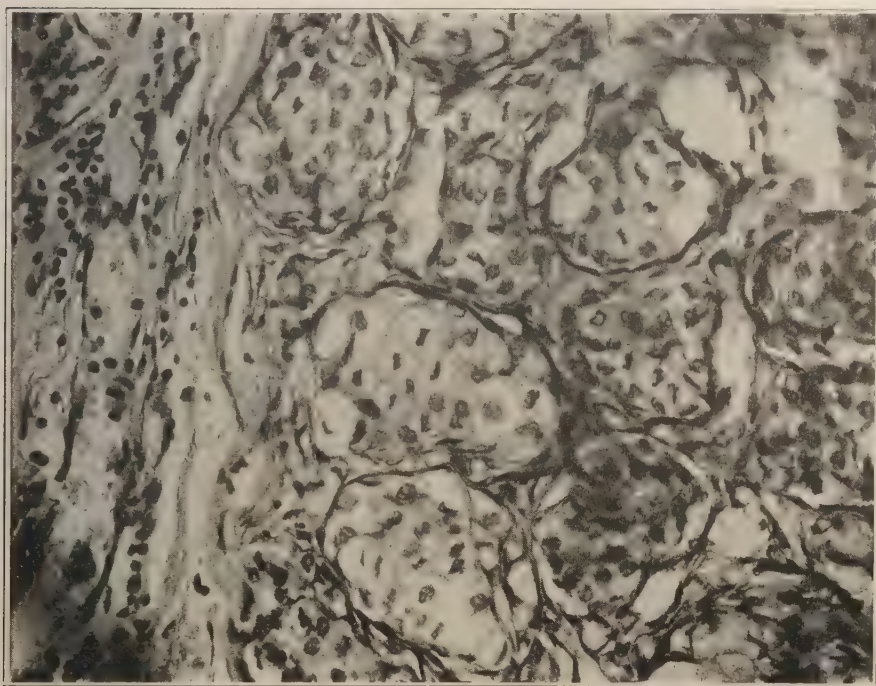
Fig. 53.—The "blasse-epithelzellen" now appear as transformed and atrophic cells of the acini of the mammary lobule, the framework of which shows well. The deformed and flattened decadent nuclei must not be mistaken for mitotic figures. The cause of the swelling and pallor of the cells is not known.

breasts, but that cases containing cysts were avoided by those collecting the material, as it was especially stipulated that only normal breasts were desired, and naturally breasts containing cysts were regarded as abnormal. The only usefulness of the material collected, as far as the study of cysts is concerned, is an opportunity to discover the probable sources of cyst formation.

Cyst formation is referable to secretion or exudation associated with retention from obstruction. If the obstruction is complete, the amount

of secretion or exudation necessary to form a cyst need be very small; if incomplete, it must be larger in proportion to the opportunity for outflow, in order that it can accumulate. Cysts resulting from complete obstruction must be but slightly variable, growing larger as fluid is added to their contents, smaller if it is absorbed, or remaining unchanged if neither condition occurs. Cysts following incomplete obstruction may vary considerably according to the additions and subtractions that may occur in their contents.

The secretory function of the breast is not confined to the cells of its acini, but is shared by those of its ducts. It has already been shown that the first activity of the breast, the secretion of the "witch's milk"
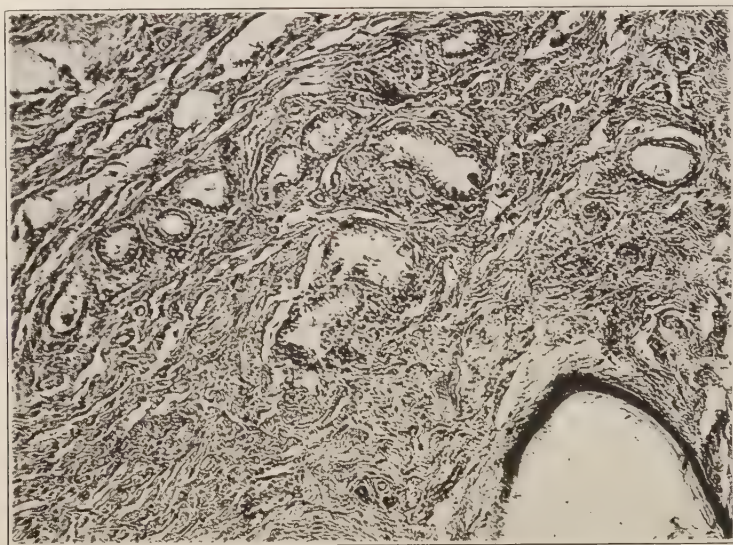
Fig. 54.—Mammary gland of a bitch that had had pups. It shows typical residual lactation acini, the epithelial cells of the larger having the typical eosinophilic cells, which, of course, cannot be shown in the illustration.

takes place from the ducts, as does the occasional serous secretion of the breasts of men, and of virgins at the menstrual periods. In the breast of the parous woman, in the intervals between pregnancy, and perhaps after the menopause, some secretion may also occur from this source, under certain conditions.

The cysts that follow involution—those of chronic cystic mastitis—usually contain clear serous fluid, and most of the distention takes place in the ducts. It may, therefore, be concluded that they arise rather from exudation than from secretion, and that the acini and milk secretion have nothing to do with them. But the involution process has everything to do with them, for it leads to the collection of varying quanti-

ties of débris of various kinds, in the ducts, occasioning partial obstruction by material that cannot be washed out by the fluid, but must be retained until its own retrogressive changes transform it to an extent permitting absorption. In the meantime, the transformation products may be the source of exudation, and their affinity for water the cause of accumulation.

Visible evidence of this can be found in almost every breast after lactation. Many of the ducts contain cylindric gelatinous formations like the tube-casts common in the kidney in certain diseases. In others there are cylinders containing an admixture of what appear to be colostrum corpuscles; in still others collections of fatty granules. Occasional ductlike spaces are found to be filled solidly with peculiar-appearing pale cells, the "Blasse-epithelzellen" of Borst and Wohlsecker. These have excited considerable interest from time to time, and various speculations have been indulged in, in an attempt to account for them. Nearly all pathologists seem to conclude with the assumption that they are evidences of proliferative activity on the part of the epithelial cells, and are indicative of impending malignant change.

This seems to be a misinterpretation. Such appearances when present in the normal sections seemed not to arise through the proliferation of cells within ducts, but through the decadence of cells of acini in process of involution. In those cases in which involution proceeds without any increase in the periductal tissue, and the partitions between the neighboring acini fail to recover from the attenuation depending on the extension to which they are subjected during the full lactation hypertrophy, the epithelial cells, not being crowded and condensed by the retraction of the interacinar partitions, nor through the proliferation of the periductal tissue, seem sometimes to enlarge and become pale. The substance of an entire lobule becomes a pale mass surrounded by the interlobular tissue against which it seems to abut with a definite outline. The impression is easily mistaken for a duct filled with epithelial cells. In reality it is a lobule surrounded by perilobular tissue. A close examination with a high power lens will frequently show the structure to be composed of groups of cells corresponding to acini, the central lumen of which is no longer visible because of the enlargement and altered character of the cells.

The seminecrotic remnants of the centrally situated cells of the residual lactation acini, together with the remnants of the intermediate partitions, frequently form considerable accumulations in their spaces, and may be followed by cystic distention just as in the ducts.

An examination of many breasts shows these appearances following involution: (1) occasional pin-head sized cysts; (2) numerous pin-head sized cysts scattered throughout the breast; (3) pin-head sized cysts collected in groups in some part of the breast; (4) pea or marble

sized cysts occurring according to one of the above described plans of distribution; (5) cysts similar to those described above in size and distribution, but filled wth darker fluid, some reddish, some chocolate; (6) single or divided cysts as large as hen's eggs, usually filled with clear serous fluid.

It seems to be the cysts that are the chief factors in calling the attention of the patient to the fact that there is something unusual about the breast. And it is easy to understand that this is probably the result of the pressure exerted by the cyst in its growth. The degree of sensory disturbance may well be in proportion to the composition of the stroma of the organ. If it is largely fatty, or if there are large quantities of the mucinoid tissue, the pressure may scarcely be felt; but if it is more fibrillar, and, therefore, less distensible, the enlarging cyst may call attention to itself through sensitiveness or pain.

The induration of the tissue adjacent to the cysts can easily be accounted for by the compression and condensation of the surrounding stroma. The occurrence of the cysts in certain quadrants of the breast can be explained on the assumption that those portions did not drain so well as others, so that contents were retained with the unfavorable consequences, retardation of involution and the formation of residual lactation acini, etc.

The cysts are of no significance in the occurrence of malignant change. It is true that occasional cysts are found, in the wall of which a cancer is situated; but this is to be looked on as an accident of association. The cyst and the cancer were both there, growing side by side, and as each enlarged, the cancer came eventually to trespass on the wall of the cyst. The relation is the same as that of cancer to residual lactation acini.

CONCLUSIONS

1. The breasts of young virgins are composed of a stroma of pure fibrillar tissue which shows an increasing mucinoid transformation with increase of years. Into the stroma, adipose tissue begins to find its way toward middle life, increasing until in old age the stroma is largely fatty. The parenchyma of the virgin breast always contains many canellated ducts. It may be without lobules, may contain only rudimentary lobules, or may contain well developed lobules in rare cases.

2. The mammary lobule develops in response to stimuli that may be either local or general. Pregnancy is its chief source, and it seems to be only under its influence that full lactation hypertrophy is reached. The lobules arise through budding from the ducts as determined by the stimuli. At any stage of development, the disappearance of the stimulus is followed by retrogression or involution of the lobule, whether throughout the breast or locally.

3. The lobules constituting the parenchyma of the breast in different pregnancies are not necessarily the same. There is some reason to suppose that for each pregnancy there is a different crop of lobules.

4. Involution, the atrophy of the no longer needed lobules is a complicated process whose details vary in different individuals, in the different breasts of the same individual, and in different parts of the same breast, according to local and general conditions.

5. One of the most important sources of the modification of involution is retention of secretion. Its effect is in proportion to its extent and distribution, and is without regularity.

6. Its most striking result is the appearance of residual lactation acini.

7. Residual lactation acini are harmless decadent structures having no significance in respect to the subsequent appearance of malignant disease.

8. The accumulated cellular and amorphous débris resulting from involution sometimes obstructs the outlets of the ducts and acini, leading to retention of secretion and exudation of fluid with cyst formation. The cysts may result from dilatation of either the ducts or the residual lactation acini.

9. The cysts may be of a size varying from that of a pin-head to a hen's egg and may be single or multiple, uniformly disseminated, or collected in groups. They usually have smooth walls and clear serous contents.

10. The pressure exerted on the surrounding tissue by the growing cyst gives rise to sensory disturbances that vary in intensity according to the firmness or softness of the stroma. In a breast with stroma largely mucinoid or adipose, they may occasion no symptoms.

11. The cysts are benign and harmless. If they become large their excision may be indicated to make the patient more comfortable.

12. Cancer cysts are not specific entities. They are the result of the accidental coexistence of cysts and cancer in the same breast. Original contiguity followed by increase in the size of each determines final continuity.

13. The so-called chronic cystic mastitis is not inflammatory, and is not a pathologic entity; it is nothing but a result—or at most—a perversion of involution.

14. It would, therefore, be desirable to abandon the term, and call the condition "cystic disturbance of the breast," or if it seems better to retain one of the older designations, that of Warren—"abnormal involution"—is probably least objectionable. The only difficulty lies in clearly defining when the process of involution can be said to become abnormal, when it is so diversified.

15. The term "adenoma" should be used only when speaking of the encapsulated tumors of the breast. Parenchymatous increases of unencapsulated or diffused form are hypertrophies and not related to tumors.

16. There is no "cyst adenoma" of Schimmelbusch. The term is objectionable because it makes it appear as though a tumor existed where no tumor is. The appearance on which the name depends is that result of involution to which the name residual lactation acini has here been given, and which can easily be found in one fourth of all breasts that have lactated.

STUDIES ON ANEURYSM

I. GENERAL STATISTICAL DATA ON ANEURYSM

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BALDWIN LUCKE, M.D., Dr.P.H.

AND

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PHILADELPHIA

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MARION HAGUE REA, A.B., M.D.

PHILADELPHIA

This paper is to serve as an introduction to a series of studies dealing with aneurysm; it contains general statistical data on the incidence, location, sex, age, race, number and recorded diagnoses of 321 aneurysms studied postmortem at the Philadelphia General Hospital and the Hospital of the University of Pennsylvania. These data are compared with similar publications from pathologic and clinical sources, so that the sum total of aneurysm on which certain phases of this investigation were undertaken is well above 3,000. Osler's [1] conception of an aneurysm, "a tumor containing blood in direct contact with the cavity of the heart, the surface of a valve, or the lumen of an artery," has been adopted; and although, as Dr. Osler points out, this definition does not include every condition now spoken of as an aneurysm, it covers the lesions studied in this paper. We have limited ourselves to aneurysm of the heart and its valves, and of the aorta and the arteries within the body cavity ("intracorporeal" aneurysms). Aneurysms of the peripheral and of the intracranial vessels are not here included.

GENERAL INCIDENCE; RELATIVE FREQUENCY IN DIFFERENT COUNTRIES

In the Philadelphia General Hospital, protocols of postmortem examination have been kept since 1867,

1. Osler, William, and McCrae, Thomas: Modern Medicine, Philadelphia, Lea & Febiger 4: 472, 1915.

in the Hospital of the University of Pennsylvania since 1875. Some 12,000 necropsies have been recorded (up to November, 1916), of which 10,600 were held at the former institution.

In the entire series, 268 subjects presented 321 intracorporeal aneurysms. The data appertaining to frequency, age, sex and race are based on the number of patients and not upon the number of aneurysms. In 2.2 per cent. of patients coming to necropsy, aneurysms were found. However, since only one out of every 6.4 patients dying at the Philadelphia General Hospital was examined postmortem (this being the average for the seventeen years ending in 1916), an accurate conception of the frequency of aneurysms in the living patient cannot be obtained.

Yet, in general, these statistics show that aneurysms are not uncommon at these two hospitals, one of which, as a teaching institution, favors such admissions, while the other is the largest charity hospital in the United States.

It has long been recognized that the frequency of aneurysms differs in various localities. Hence statistical data based on postmortem examination have been selected for comparison from American, English, Scandinavian, German and Austrian publications. Table 1 shows that, in 160,145 postmortem examinations, 1,452 aneurysms were discovered; that is, one aneurysm occurred in every 111, or 0.9 per cent. patients examined postmortem. These figures are only relative, for it must be remembered that a certain proportion of patients possess multiple aortic aneurysms; however, the total number of postmortems and of aneurysms recorded is so large that fair conclusions may be drawn. Since most writers have confined themselves to statistical study of aortic aneurysms, we have in Table 1 compared the relative frequency of aortic aneurysms only.

It has been remarked that of the Caucasian races, the Anglo-Saxon is a more frequent sufferer from aneurysm that the Teuton, and our figures support this belief. Thus, for the United States the average incidence in persons examined postmortem is one aortic aneurysm in forty-one; for Great Britain, one in seventy-four; for the Scandinavian countries, one in 109, and for Austria and Germany, one in 198.

TABLE 1.—RELATIVE INCIDENCE OF AORTIC ANEURYSM IN DIFFERENT COUNTRIES

Country	Author	Year of Publication	Source and Date	Number of Necropsies	Number of Aortic Aneurysms Found	Frequency
United States	Lemann	Am. J. M. Sc. 152:210 (Aug.) 1916	Charity Hosp., La., 1865-1914	2,000	67	1 in 29
	Osler	Modern Medicine 4:472, 1915	Johns Hopkins Hosp.	2,200	49	1 in 45
	Lucke and Rea	1921	Phila. Gen. Hosp., 1867-1916; Univ. of Pennsylvania, 1875-1916	12,000	278	1 in 43
Total				16,200	394	1 in 41
Great Britain	Nunnelly	Aneurysm of Abdominal Aorta, 1906	St. George's Hosp., London, 1841-1865	17,872	166	1 in 107
	Bryant	Clin. J. 23:71, 1903	Guy's Hosp., London, 1854-1900	18,678	325	1 in 57
Total				36,550	491	1 in 74
Scandinavia	Rash	Arch. f. Dermat. & Syph. 47:15, 1899	Kommune Hosp., Kopenhagen, 1892-1896	3,165	28	1 in 113
	Dahlen	Ztschr. f. klin. Med. 58:163, 1907	Seraphim Hosp., Stockholm, 1897-1906	2,325	22	1 in 105
Total				5,490	50	1 in 109
Germany and Austria	Bosdorff	Ueber Häufigkeit und Vorkommen der Aneurysma, 1899	Kiel Path. Inst., 1873-1888	5,352	28	1 in 191
	Bauler	Untersuchungen ueber die Rolle der Syphilis, etc., Basel, 1908	Basel Path. Inst., 1888-1908	9,570	58	1 in 165
	Vix	Zur Lehre ueber die Aorten-aneurysmen, Erlangen, 1904	Erlangen Path. Inst., 1862-1903	9,792	38	1 in 257
	Müller	Zur Statistik der Aneurysmen, Jena, 1902	Jena Path. Inst., 1865-1900	10,360	69	1 in 150
	Borowsky	Die Perforations-richtung der Aneurysmen der Aorta thoracica, Breslau, 1910	Breslau Path. Inst., 1892-1909	19,646	66	1 in 297
	Emmerich	Ueber die Häufigkeit der inneren Aneurysmen in München 1888	München Path. Inst., 1876-1888	8,669	52	1 in 166
	Juda	Die Beziehungen zwischen Aneurysmen und Tuberkulose, Erlangen, 1892	Städt. Krankenh., Dresden, 1851-1862; Erlangen Path. Inst., 1862-1891	8,871	35	1 in 253
	Coninotti	Wien. klin. Wchnschr. 14:843, 1901	Städt. Kankenhaus Triest	26,495	176	1 in 149
	Eppinger	Praktische Heilkunde 113:1; 114:1, 1872	Prager Path. Inst., 1868-1871	3,149	15	1 in 210
Total				101,905	517	1 in 198
Grand total				160,145	1,452	1 in 111

Again, it must be emphasized that in the United States only a certain percentage of patients are examined postmortem, while in Austria and Germany postmortem examination of hospital patients is the rule. Clinical observations also support the view that aneurysm is more frequently encountered in the United States and Great Britain than elsewhere. Thus, Osler [1] states that in the British army home contingent with a strength of 118,224 (in 1905) there were eighteen deaths from aneurysms; in Germany (1904-1905), with an army of 555,777, there were four. Wolpert [2] states that in 74,744 patients treated at the Medical Clinic of the University of Berlin (1895-1905), aortic aneurysm was diagnosed in fifty-five instances, i. e., one person in 1,359. Eichhorst [3] (Medical Clinic, Zürich, 1884-1901) found twenty-eight patients with aortic aneurysm among 33,377 patients, i. e., one in 1,200. Dahlen [4] reports that in the Seraphim Hospital in Stockholm, twenty-two patients with aortic aneurysms were discovered among about 15,000 inmates (1897-1906); i. e., one in 790. Very different figures are obtained in British reports: Browne [5] mentions that at St. Bartholemew's Hospital (1867-1883) with a yearly average of 5,000 inpatients (i. e., 90,000) there were 228 with aortic aneurysm, i. e., one in about 350. Osler [6] gives the incidence of aortic aneurysms in 24,363 admissions to the medical wards of the Johns Hopkins Hospital (1889-1909) as 231; i. e., one in 105 patients; and lastly, Lemann [7] finds forty-seven patients with thoracic aneurysms in 15,513 outpatients at the Touro Infirmary, i. e., one in 300.

Therefore, both from clinical and from necropsy data, it seems fair to conclude that aortic aneurysm is more frequently found in the United States and Great Britain than on the European continent, or at

2. Wolpert, R.: Ueber die Haüfigkeit und Enstehung des Aorten-aneurysma, Berlin, 1905.
3. Eichhorst, H.: Handbuch der speziellen Pathologie und Therapie, Ed. 6, Berlin, Urban and Schwartzenberg, 1904, p. 284.
4. Dahlen, B.: Ueber einen Fall von Aorten-Aneurysma, mit Durchbruch in den linken Vorhof nebst einigen Bemerkungen über Aorte-aneurysma, die fibroese Aortitis and Lues, Ztschr. f. klin. Med. 58: 163-196, 1907.
5. Browne, Oswald: Aneurysms of the Aorta with Especial Reference to Their Position, Direction and Effect, Cambridge, 1885.
6. Osler, William: Syphilis and Aneurysm, Brit. M. J. 2: 1509-1514, 1909.
7. Lemann, T. T.: Aneurysm of the Thoracic Aorta: Its Incidence, Diagnosis and Prognosis, Am. J. M. Sc. 152: 210-222 (Aug.) 1916.

least in the Teutonic countries. To explain this is
more difficult. No doubt vascular syphilis is the under-
lying cause for the great majority of aortic aneurysms,
and it may well be that the type of syphilis which
tends particularly to involve the vascular system is
more common in certain countries than in others.
Whether there exist strains of spirochete having a
selective affinity for the cardiovascular apparatus has
not as yet been determined; but at least the researches
of Marie and Levaditi [8] indicate that certain strains
of spirochete produce lesions of the brain and cord,
while others affect chiefly the cutaneous surfaces.
We have learned in the last few years that most
pathogenic bacteria are not entities but groups con-
sisting of many types (streptococcus group, pneu-
mococcus group, typhoid group, etc.), and that the
different members of such groups behave in dis-
similar fashion. Clinical experience has demonstrated
that some of the many forms of syphilis occur rarely
in certain countries and among certain races. Of the
latter, an example is the incidence of tabes dorsalis
and aortic aneurysm, among the white and negro
population of this country. Tabes is fairly common in
white peoples, but quite rare among negroes. Indeed,
only in the last few decades has locomotor ataxia been
observed at all in full blooded blacks.[9] On the other
hand, the proportionate incidence of aortic aneurysm
is far greater in the negro than in the white population.

All such facts may point either to the existence of
different spirochetal strains possessing selective affini-
ties and being particularily prevalent in certain coun-
tries or races, or to the predisposing influence on the
vascular structures of racial charteristics.

LOCATION

The location of the aneurysms, the marked pre-
ponderance of aortic over nonaortic aneurysm, and
the comparative infrequency of aneurysm of the vari-
ous aortic branches is shown in Table 2. The arch of
the aorta is most frequently involved, next the abdomi-

8. Marie, A., and Levaditi, C.: La paralysie générale est due à un
tréponème distinct de celui de la syphylis banale, Rev. de méd. **37:**
193, 1920.
9. Lucke, Baldwin: Tabes Dorsalis: A Pathological and Clinical
Study of Two Hundred and Fifty Cases, J. Nerv. & Ment. Dis. **48:**
393-410 (May) 1916.

nal, and somewhat less frequently the thoracic aorta.
Of the aortic branches, the innominate and splenic
arteries are most often the seat of aneurysm. These
findings in general correspond to most statistical
reports, but are greatly at variance with the work of
Edward Crisp,[10] "Table of 551 spontaneous aneurysms
selected indiscriminately from the British medical and
surgical journals, from the year 1785 to the present
time" i. e., 1844). This writer in 1851 published
a little known appendix [11] to his monograph in which
he adds data (from the same sources as in his first

TABLE 2.—LOCATION OF THREE HUNDRED AND TWENTY-
ONE ANEURYSMS

Heart and its valves		15
Heart	13	
Heart valves	2	
Aorta		278
Sinus of Valsalva	10	
Ascending arch	62	
Junction of ascending and transverse arch	23	
Transverse arch	46	
Descending arch	42	
Entire arch	19	
Arch (unclassified)	4	
Entire aorta (dissecting aneurysm)	1	
Thoracic aorta	31	
Abdominal aorta	40	
Aortic branches (and pulmonary artery)		28
Ductus arteriosus	1	
Coronary artery	1	
Innominate artery	13	
Left carotid artery	1	
Pulmonary artery	1	
Superior mesenteric artery	1	
Celiac axis	1	
Splenic artery	6	
Renal artery	2	
Internal iliac artery	1	

paper) on 151 aneurysms, bringing the total number
of his cases to 702. Since his appendix is now some-
what inaccessible, the general statistical data as to loca-
tion of the aneurysms are here cited: thoracic aorta,
241; pulmonary, 2; abdominal aorta and its branches,
73; common iliac, 2; popliteal, 182; posterior tibial,
21; innominate, 22; carotid, 28; cerebral, 13; temporal,
1; ophthalmic, 1; subclavian, 25; axillary, 24; sub-
scapular, 1; brachial, 1. Crisp's data are mainly
based on clinical reports, selected, as he states, "indis-
criminately"; hence not even approximate deductions

10. Crisp, Edward: A Treatise on the Structure, Diseases and
Injuries of the Blood Vessels, London, J. Churchhill, 1847.
11. Crisp, Edward: Appendix to the Treatise on the Structure, Dis-
eases and Injuries of the Blood Vessels, London, H. Teape & Son, 1851.

as to the relative occurrence and distribution of aneurysms can be drawn from them, and the quotation of his tables without further qualification can only give a wrong impression as to the location of aneurysms.

The most striking feature of his tables is the extraordinarily large number of aneurysms of the peripheral arteries; in the 12,000 postmortem records on which the present study is based, less than a dozen of such aneurysms are recorded; and, judging from other clinical and postmortem statistics, aneurysms of the peripheral vessels are relatively uncommon. Crisp's statistics, are, however, not to be undervalued, for they contain a wealth of information.

AGE

Aneurysm may occur at any age, but it is most frequently found in early middle life. The incidence of age, as recorded in our series in 247 patients, is given

TABLE 3.—INCIDENCE OF AORTIC ANEURYSM ACCORDING TO AGE

Age	No. of Cases
Under 20 years	1
From 20 to 29 years	9
30 to 39 years	32
40 to 49 years	81
50 to 59 years	60
60 to 69 years	42
70 to 79 years	18
80 to 100 years	4

in Table 3. The youngest patient in the series was 12 days old; the oldest, 91 years.

The table shows that aneurysm may occur at any age, but that before the twentieth year it is very uncommon. Beginning at this age the curve of incidence rises gradually, to ascend somewhat sharply in the fourth decade to its maximum; there is a slight fall during the fifth decade, and from there on a steady decline.

The average duration of life after the clinical recognition of an aneurysm has been variously estimated and, as may be expected, no uniformity of opinion has been reached; but, in general, it is thought that the expectation of life in the average case is but little over two years. Hall [12] carefully analyzed thirty-five

12. Hall, F. de H.: Intrathoracic Aneurysm, Lancet 1: 843, 869, 945, 1913.

private cases (of intrathoracic aneurysm) and found that in twenty-seven of these the average duration of life after diagnosis was established was a little over two years and eight months. He has seen, however, a patient living for ten years. Nunnelly [13] finds that the average course of aneurysms of the abdominal aorta, from the first appearance of the symptoms, extends over from thirteen to fifteen months. Bosdorff [14] places the usual duration as from one and a half to two years; Emmerich, as from twelve to eighteen months. Crisp,[15] on the other hand, believes the average duration of life to be from eight to ten years. Thus one might quote a considerable number of writers. It is most probable that the duration of life depends entirely on the individual case, and on the care and treatment the patient receives.

As will be pointed out, the majority of aneurysm patients die from a disease independent of the aneurysm; in our series, only about one third died from rupture.

In Table 4 the age incidence is collected from various pathologic as well as from clinical sources. In all, 4,217 aneurysm cases are tabulated. The most frequent age period given by the different writers varies considerably.

The statistics are tabulated under four headings: (a) aortic aneurysms from postmortems; (b) aortic aneurysms collected from clinical sources and from the literature; (c) all aneurysms (including aortic) from postmortems, and (d) all aneurysms (including aortic) collected from clinical sources and from the literature. As far as aortic aneurysms are concerned, there appear to be noteworthy differences in the most frequent age periods given, the majority of cases occurring between the ages of 35 and 55. In the figures dealing with aneurysms in any location (this includes aortic aneurysms) more advanced age periods are stated by some authors. Thus, Bosdorff [14] gives from 60 to 80 years, and Juda [16] from 60 to 70 years as the most frequent

13. Nunnelly, F. P.: Aneurysm of the Abdominal Aorta, Oxford, 1906.
14. Bosdorff, Ernst: Ueber Häufigkeit und Vorkommen der Aneurysma, Kiel, 1899.
15. Crisp (Footnotes 10 and 11).
16. Juda, David: Die Beziehungen zwischen Aneurysmen und Tuberkulose, Erlangen, 1892.

TABLE 4.—SEX-AGE INCIDENCE

Author	Location of Aneurysm	No. Cases	Males	Females	Ratio M to F	Most Frequent Age Period
(a) Aortic aneurysms (collected from pathologic-anatomic sources)						
Biggs[*]	Aorta	34	27	7	3.9 to 1	Av. 44.3
Lemann[7]	Thor. aorta	47	35	12	2.9 to 1	35-55
Bauler[†]	Aorta	58	37	21	1.5 to 1	Not stated
Vix[20]	Aorta	37	28	9	3.1 to 1	40-50 av.
Müller[17]	Aorta	69	51	18	2.6 to 1	40-60
Kröger[21]	Aorta	48	38	10	3.8 to 1	Av. 52.2 M. 51.3, F. 56.1
Emmerich[18]	Aorta	51	35	16	2.2 to 1	40-60
Rash[†]	Aorta	28	21	7	3 to 1	40-60
Bryant[†]	Abd. aorta	54	50	4	12.5 to 1	30-40
Browne[5]	Aorta	88	74	14	5.2 to 1	35-55
Browne[‡]	Aorta	140	122	18	6.7 to 1	35-55
Hall[12]	Aorta	98	89	9	9.9 to 1	35-55
Dahlen[4]	Aorta	27	20	7	2.9 to 1	40-55
Total		779	627	152	4.1 to 1	
(b) Aortic aneurysms (collected from clinical sources, or from literature)						
Crisp[15]	Aorta	314	261	53	5 to 1	30-40
Borowsky[†]	Aorta(rupt.)	175	150	25	6 to 1	40-50
Maximoff[19]	Aorta	303	252	51	4.9 to 1	40-50
Maximoff[19]	Aorta	41	29	12	2.5 to 1	40-60
Wolpert[2]	Aorta	55	22	33	0.7 to 1	Av. 53.3 M. 52.1, F. 50.7
Hall[12]	Thor. aorta	188	160	28	5.5 to 1	Not stated
Total		1,076	874	202	4.3 to 1	
(c) All aneurysms (collected from pathologic-anatomic sources)						
Bosdorff[14]	All aneur.	94	51	43	1.2 to 1	60-80
Lucke & Rea	All aneur.	247	200	47	4.3 to 1	40-60
Müller[17]	All aneur.	183	108	75	1.4 to 1	50-70
Emmerich[18]	All aneur.	58	39	19	2.1 to 1	40-60
Cominotti[†]	All aneur.	181	150	30	5 to 1	40-50
Juda[16]	All aneur.	48	31	17	1.8 to 1	60-70
Lidell[§]	All aneur.	243	200	43	4.6 to 1	30-40
Von Schrötter[#]	All aneur.	220	146	74	2 to 1	40-50
Total		1,274	925	348	2.7 to 1	
(d) All aneurysms (collected from clinical sources, or from literature)						
Crisp[15]	All aneur.	702	624	78	8 to 1	30-50
Lebert[¶]	All aneur.	386	296	90	3.2 to 1	35-45
Total		1,088	920	168	5.4 to 1	
Grand total		4,217	3,346	870	3.8 to 1	

Crisp, Cominotti and von Schrötter stated only the male-female ratio; from this the actual numbers were calculated.

* Biggs, H.: Some Observations on Aortic Aneurysms, with a Report of Thirty-Four Cases with Autopsies, Am. J. M. Sc. 97 : 219, 1889.

† Reference appears in Table 1.

‡ Browne, Oswald: Aneurysm of the Aorta, London, H. K. Lewis, 1897.

§ Lidell, John A.: On Internal Aneurysm, and Its Relation to Sudden Death, Am. J. M. Sc. 53 : 46-81, 1867.

Von Schrötter, L.: Erkrankungen der Gefässe, in Nothnagel: Spezielle Pathologie und Therapie, Vienna, Alfred Holder, 1901, 15, Part III.

¶ Lebert, H.: Krankheiten der Blut- und Lymph-gefässe, in R. Virchow's Handbuch, Ed. 2, Vol. V, Erlangen, 1867, F. Enke; also Traité de l'anatomie pathologique, I, Paris, J. B. Balliere, 1857.

age periods, but an analysis of the material on which their data are based reveals that both writers included a considerable number of small aneurysms of the cerebral arteries.

Aneurysms occur at different age periods in whites and blacks, in males and females. In Table 5 the average ages of these various groups are shown. The average age at which white persons suffering with aneurysm came to necropsy was 54.4 years, and only 45.3 years for negroes. A somewhat less marked age difference is shown to exist between men and women, the average of the former being 46.9 years, of the latter 52.8 years.

Similar difference in ages exists between white males and white females, and between black males and

TABLE 5.—INCIDENCE OF RACE, SEX, AGE, AND RACE-SEX RATIO

Race or Sex	Number Recorded	Average Age	Race-Sex Ratio
White..............	173	54.4	2.3 whites : 1 negro
Negroes............	74	45.3	
Males..............	200	46.9	4.2 males : 1 female
Females...........	47	52.8	
White males........	134	51.3	3.4 white males : 1
White females......	39	57.6	white female
Negro males........	66	42.5	8.2 negro males : 1
Negro females......	8	48.1	negro female

black females, while between white females and black males the marked discrepancy of fifteen years is seen.

SEX

In our series there are 200 males and forty-seven females (sex not recorded in twenty-one instances); this gives a ratio of 4.2 males to 1 female. Table 4 shows that practically all writers have found a similar preponderance of the male sex. The sex incidence has been grouped under four headings: (*a*) aortic aneurysms from postmortem statistics; (*b*) aortic aneurysms from clinical sources, or collected from the literature; (*c*) all aneurysms (including aortic aneurysms) from postmortem statistics, and (*d*) all aneurysms (including aortic aneurysms) from clinical sources or compiled from the literature. The total number of aneurysms collected in the table is 4,217; of these, 3,346 occurred in males and 870 in females,

giving a ratio of 3.8 males to one female. Several writers (Bosdorff,[14] Müller,[17] and Juda[16]) record an unusually large number of females in their series; the same writers also give the most frequent age period at a very advanced time of life (i. e., from 50 to 80). Analysis of their reports shows that a relatively small number of aortic aneurysms was included, and that their figures are based on a relatively large percentage of aneurysms of the aortic branches and the cerebral vessels. One may, perhaps, draw the conclusion from the data that aneurysms of such arteries are somewhat more common in females than in males. The greater longevity of women, in general, may account for the advanced age periods given. Emmerich,[18] whose statistics (Pathological Institute, Munich) show an unusual proportion of females, explains this by stating that in Munich women did more hard manual labor than elsewhere. All these, however, are exceptions, and it may be stated that, in general, aneurysm occurs four times more frequently in the male than in the female sex.

RACE

Aneurysm seems to be particularly common in the negroes. In our series there are 173 whites and seventy-four negroes, a ratio of 2.3 whites to one negro. In 5,000 admissions to the medical wards of the Philadelphia General Hospital the ratio of whites to negroes was fifteen whites to one negro. Osler[1] gives the ratio for aneurysm as 2.6 white to one negro, while the proportion of white to colored patients in the wards (of the Johns Hopkins Hospital) was as four white to one negro. Lemann,[7] however, finds the difference between whites and negroes not at all marked. From his table on thoracic aneurysm it appears that among the males the aneurysms were about as frequent in white men as in negroes, while the negro female cases were relatively three times as frequent as the white female one. Our own figures, however, are similar to Osler's, and show the greater

17. Müller, Ernst: Zur Statistik der Aneurysmen, Jena, 1902.
18. Emmerich, Otto: Ueber die Häufigkeit der inneren Aneurysmen in München, München, 1888.

relative frequency of aneurysm in the negroes. The ratio of occurrence and other data are shown in Table 5.

NUMBER OF ANEURYSMS

While it is generally known that small aneurysms of the cerebral arteries are commonly multiple, the fact that more than one large aneurysm of the aorta or its branches occur not infrequently is often overlooked in clinical examinations. Thus, it is not unusual to find only one aneurysm diagnosed, yet two or more are discovered at necropsy. If, for instance, an aneurysm of the ascending arch coexists with one of the abdominal aorta, one or the other is frequently overlooked, often because no effort is made to search for multiple aneurysms. In our series, multiple aneurysms occurred in fifty three patients; that is, one in every five patients with aneurysm had more than one such lesion.

In detail:

In 41 patients, 2 aneurysms were present.
In 10 patients, 3 aneurysms were present.
In 1 patient, 4 aneurysms were present.
In 1 patient, 5 aneurysms were present.

These were chiefly aneurysms affecting the aorta, but in several instances an aortic aneurysm coexisted with an aneurysm of one of the aortic branches.

DIAGNOSIS

Aneurysms frequently escape clinical detection. A glance through the postmortem protocols tabulated by Bosdorff,[14] Browne,[5] Crisp,[15] Maximoff,[19] Dahlen,[4] Vix,[20] Kröger,[21] Przygode[22] and other authors shows that a very high percentage of aneurysms discovered at the necropsy table was not recognized clinically. Lemann[7] recently discussed the diagnosis, and failure to diagnose, of aneurysms, and cites Sir William Osler's dictum that there is no disease more conducive to clinical humility than aneurysm of the aorta.

19. Maximoff, N.: Beitrag zur Statistik der Aneurysmen, München, 1910.
20. Vix, K.: Zur Lehre über die Aorten-aneurysmen, Erlangen, 1904.
21. Kröger: Statistik der Aorten-aneurysmen nach den Sektions-protokollen von 1872-1899, Kiel, 1901.
22. Przygode, Paul: Ueber die Rückwirkung der Aorten-aneurysma aufs Herz, Giessen, 1909.

The clinical diagnoses recorded on the postmortem protocols in our series are given in Table 6.

In this series the correct diagnosis, i. e., aneurysm, was recorded in only 43 per cent. of the cases. It must be remembered, however, that these records began in 1867, before the days of modern diagnostic methods. The conditions most frequently mistaken for aneurysm are given in Table 6.

SUMMARY

This paper contains a statistical analysis of 321 aneurysms of the heart and its valves, the aorta and the aortic branches.

1. In 12,000 postmortem examinations at the Philadelphia General Hospital and the Hospital of the

TABLE 6.—CLINICAL DIAGNOSES RECORDED IN A SERIES OF TWO HUNDRED AND SIXTY-EIGHT CASES WITH ANEURYSMS

Diagnoses	Number of Cases
Aneurysms	95
Asthma	8
Chronic endocarditis	21
Chronic myocarditis	17
Pulmonary tuberculosis	9
Mediastinal tumor	2
All other diagnoses	71
Not recorded	45

University of Pennsylvania, 321 "intracorporeal" aneurysms occurred in 268, or 2.2 per cent., of patients examined postmortem.

2. Comparison of statistics shows that aneurysms are more frequent in the United States and Great Britain than in the Teutonic countries.

3. The aorta is more often involved; the various aortic branches are relatively rarely the seat of aneurysms.

4. The most frequent age period for aortic aneurysm is the fourth and fifth decades.

5. Aneurysm occurs at an earlier age in the negro than in the Caucasian race.

6. Aneurysm occurs about four times more frequently in males than in females.

7. Aneurysm is relatively more common in the negro than in the Caucasian.

8. In fifty-three patients (about 20 per cent.), multiple aneurysms were found.

9. The clinical diagnosis was made in 43 per cent.

REPORT OF A CASE OF SPONTANEOUS GANGRENE, SIMULATING PURPURA, DUE TO ACUTE THROMBOARTERITIS.*

By David W. Kramer, M. D.,

Philadelphia,

Demonstrator of Clinical Medicine in Jefferson Medical College;
Assistant Visiting Physician to the Philadelphia General,
Jewish and Mt. Sinai Hospitals.

When one considers the frequency of bacteremias
in the early stages of certain wellknown acute in-
fectious maladies, particularly typhoid fever and
pneumonia, as well as the various septicemias, one
cannot help being impressed with the rarity of in-
volvement of the bloodvessels themselves. Albutt,
indeed, mentions "that terrible disease as yet
wrapped up in obscurity, in which arterial trunks
are seized by an *acute arteritis* with agonizing pains
and gangrene; this thromboangeitis is not to be
confounded with the arteriosclerosis of hyperpiesis
or of decrescense." It is possible that the occur-
rence of arterial infections is not so rare as we have
been led to believe. Some cases, no doubt, are not
recognized; others are mistaken for purpura or gan-
grene, the diagnosis being based upon clinical mani-
festations, rather than upon the underlying etiologi-
cal and pathological conditions. Such diagnoses
make it difficult to collect data and statistics which
might aid us in throwing some light upon this ob-
scure condition.

At the Philadelphia General Hospital we observed
a case closely resembling purpura hemorrhagica, in
which gangrene of the foot developed. The clinical
diagnosis of acute thromboangeitis with gangrene

was confirmed by the laboratory after microscopic studies were made of sections of the bloodvessels in the amputated leg.

I am indebted to Professor Solomon Solis Cohen for permission to report this case, which became of interest to his staff through his interest in it, coupled with the persistent refusal to accept the diagnosis of purpura hemorrhagica.

CASE.—E. H., white, male, eight years old, was admitted December 7, 1920, to Dr. Solis Cohen's service with a provisional diagnosis of purpura. The family history and past medical history have no bearing upon the case.

The present illness dated back one week. The mother stated that the trouble began on Wednesday night, December 1, 1920, when the boy complained of headache after supper. During the night he was restless and feverish, and vomited twice. There was no diarrhea, no convulsion. Headaches persisted on the following day. The patient was very pale. On Friday, purple blotches appeared on the knees and outer aspects of both legs; these blotches later showed themselves on the body as well. The limbs were said to "feel stiff and sting."

The physical examination revealed a glistening, red, injected pharyngeal mucous membrane; enlarged and injected tonsils; several small ulcerations on the tip of the tongue. On the chest were a few irregularly shaped pigmented patches with reddish borders. The lungs were negative. No murmur was heard in the heart, but the first sound was impure.

The extremities showed irregularly shaped and variously sized patches of discoloration over the lower extremities and a few in the upper limbs. These patches varied in intensity from a faint purplish hue to a true hemorrhagic condition with sloughing. The left leg was the worse, and showed confluence of some extensive areas. The left foot was blue, the toes cold, and bluish-black in color.

No pulsation of the dorsalis pedis could be discerned.   (See Fig. 1 and 2.)

The temperature on admission was 99° F.; later it went up to 104°.   The pulse range was from 90 to 110.   The Wassermann test was negative. The blood on admission showed 26,400 white blood cells; polymorphonuclears, eighty-one per cent.; lymphocytes, nineteen per cent.; coagulation time, two minutes and two and a half minutes; blood platelets, 328,800.

Bacteriological studies were made of the blood,

Fig. 1. Lower extremities two weeks after onset, showing purpuric extravasations and beginning gangrene of the left foot involving the toes. Note the darker areas on right thigh, showing definite evidences of tissue changes.

of the pus from the ulcerated foot, and of cultures from the throat, the mouth, and teeth.   The blood culture was sterile.   The throat culture showed streptococci.   The cultures from ulcers in the mouth showed Staphylococcus aureus, Streptococcus viridans and Micrococcus catarrhalis. The culture from the pus in the ulcerated foot contained Staphylococcus albus and a gram positive bacillus.   The urine contained at times a trace of albumin.

The patient's condition became steadily worse.

Gangrene developed in the left foot. (See Figs. 3 and 4.)

The surgeon (Dr. Loux) called in consultation, advised amputation above the knee; which operation he did on December 31st, about three and a half weeks after the patient's admission. Convalescence was slow and tedious but recovery finally ensued. When last heard from (January, 1922) the lad was robust and enjoying good health.

The amputated limb was sent to the pathological
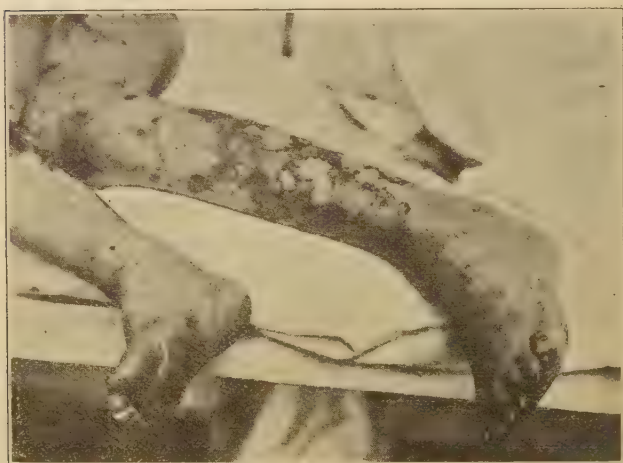
Fig. 2.—Same as Fig. 1.

laboratory of the hospital, and studied by the histologist, Dr. W. P. Belk, who reported as follows:

Nine sections were taken from the amputated limb of E. H., Surgical Series No. 1807.

The large arteries showed a thickening of the media, which was due to a moderate proliferation of fairly young connective tissue cells. There was also a moderate amount of round cell infiltration in this arterial coat. At one point one large artery showed what appeared to be a very early and

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slightly marked necrosis.   Opposite this there is a thrombus firmly attached to the intima.   The endothelial coats at this point have been lost.

In all sections the small arteries showed a more advanced pathological process.   The thickening—still chiefly of the media—was great, resulting in the narrowing of the lumina to about one third or more of the original diameter.   The fibrosis here was further developed and at points new bloodvessels could be seen within this new fibrous growth. Infiltration of lymphocytes in the arterial coats was
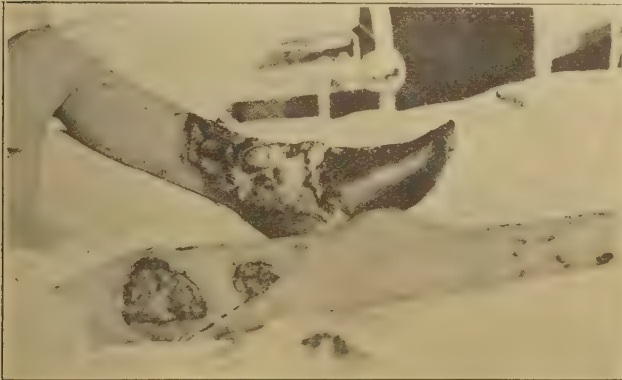
FIG. 3.—Four weeks after onset.   Sloughing and gangrene involving left foot.   Sloughing ulcerated areas on right thigh.

quite noticeable.   There was no marked perivascular, but a diffuse lymphocytic infiltration of a moderate degree throughout all tissues.   Sections from necrotic areas showed the usual picture of necrosis, with infiltration of polymorphonuclear leucocytes.

The process was definitely an infectious one of moderate chronicity, probably of a duration of several weeks.   Diagnosis: proliferative thromboarteritis.

DISCUSSION.

The diagnosis ordinarily made in cases of this type is purpura of either the hemorrhagic or the

fulminating type. Schoenlein's purpura was suggested by one physician who saw our patient. There are scattered case reports in the literature, under superficial diagnoses of purpura or gangrene, which present a clinical picture that seems to demand more careful study before we can rule out some definite underlying condition, perhaps one common to all, and represented by that found in our case.

Summarizing, we had a definite sudden onset: fever; an injected throat; and a high leucocytosis— 26,400 with a relative polymorphonucleocytosis of
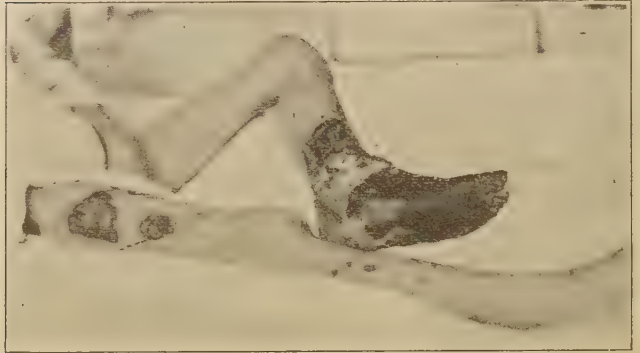
Fig. 4.—Same as Fig. 3.

eighty-one per cent. All these phenomena point to some septic condition. The fact that the blood culture was sterile does not necessarily mean that there was no bacteremia; certainly not that there was no involvement of bloodvessels; for the culture is negative, as a rule, in that recognized disease of the arteries, periarteritis nodosa.

Later the appearance of the socalled purpuric spots, of extensive areas of ecchymosis, and finally of gangrene, indicated that something had taken place in and about the bloodvessels. The fact that the blood platelets were normal, with a normal clotting time, seems to rule out, what we may call for

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distinction, the socalled true purpura, in which the hemorrhagic extravasations are said to be dependent upon some impairment of the blood clotting mechanism. Here we were evidently dealing with a more intensive condition. Areas of gangrene, which may involve an extremity, can only be attributed to some disturbance in the circulatory apparatus resulting in arterial occlusion. This occlusion may be spasmodic, as in Raynaud's syndrome, but in our case, was presumably owing to thrombus formation, originating directly from the inflamed arterial wall or from emboli which may have lodged in the vessel. If emboli, whence did they come? There was no endocarditis, there was no definite general infection —at least none that could be recognized. The throat condition seemed of importance as a possible focus of infection, but not otherwise. Attention was therefore turned to an inflammatory process involving the vessels themselves. Such inflammations, producing destruction in some cases, and occlusion in others, are known to occur. With these facts in mind diagnosis was definitely entered as acute thromboarteritis.

Arteritis has been observed in connection with such infections as diphtheria, influenza, pneumonia, typhus and typhoid fevers, scarlet fever, measles, rheumatic fever, and syphilis. It may also occur independently.

ETIOLOGY.

The exact nature of the causative agent, whether toxin or bacterium, is still an open question. In the group of cases which seem to develop independently the condition may be due to some strain of the streptococcus group. This view is favored by the frequency of sore throat and the persistent finding of some form of Streptococcus. Klotz, Bailly, Head, and Manges and Baehr report the presence of this germ somewhere in the patients whom they have studied. In our case streptococci were found in the throat and in the ulcers of the mouth. Unfor-

tunately, the blood cultures revealed nothing to help us in arriving at a definite conclusion.

The question of syphilis is always raised when dealing with diseases of the arteries. The spirochete is notorious for its influence upon the aorta and the circulatory system but it is not found necessarily in acute arteritis. However, it may be a predisposing factor by weakening the walls of the vessels, making them less resistant to bacterial invasion. It could hardly account for the clinical picture of an acute infection with septic temperature and leucocytosis.

PATHOGENESIS.

The manner in which the bacterial agent enters the vessel walls is debatable. The avenue of infection varies. The intima may be infected, a, directly, either by the microorganism or by an embolus which becomes lodged in the lumen of the vessel; or, b, indirectly, by an extension of the process from the outer coats. The media and adventitia may be the starting points, the infective agent gaining entrance by way of the vasa vasorum or perivascular lymphatics. Klotz emphasizes the importance of the perivascular lymphatics and their relation to the entrance of bacteria into and about the arterial walls.

CLINICAL COURSE.

I shall confine myself to the acute forms of arteritis which usually come on suddenly with headaches and severe pains over the region of the affected vessels. Abdominal cramps and vomiting may be present. Often there is a history of sore throat. Fever is the rule, and is ordinarily of the septic type. Commonly there is marked leucocytosis.

PATHOLOGY.

Macroscopically, there are areas of ecchymosis, necrosis and gangrene. The gangrene may appear in local areas or it may involve either an entire limb or two or more extremities. In the periarteritis

nodosa type there may be found small, hard nodules and aneurysmal dilatations along the course of the involved arteries.

Microscopically various lesions in and about the vessel walls have been described. The pathological picture differs with the type and virulence of the infection, with its chronicity and with the proximity of the area examined to the site of greatest activity—possibly the focus of infection. Any vessel may be involved but the medium sized and smaller arteries show the greatest changes.

The intima may be swollen, with proliferation. In some areas one may find thrombi resting upon the intima; in others the intima is lost. In some vessels there is complete obliteration of the lumen by a thrombus which may or may not show organization and canalization, depending upon the time of its formation. The media is nearly always affected and evidently early in the disease. In this coat one may find infiltrations of all types of cells, with thickening that may encroach upon the lumen of the artery. Later on there is found hyaline degeneration and fibrosis. The adventitia usually shows more or less cellular infiltration, especially in cases of periarteritis nodosa. In nearly all cases there is more or less cellular infiltration in the perivascular tissues.

DIAGNOSIS.

Acute thromboarteritis may be recognized by its clinical picture—sudden onset; septic temperature; severe pains; leucocytosis; hemorrhagic extravasations under the skin; areas of sloughing and gangrene; clotting time is normal or accelerated; platelets are not deficient. It is confirmed by a microscopic study of the arterial walls which should reveal the lesions already described.

DIFFERENTIAL DIAGNOSIS.

Purpura fulminans and other types of purpura must be ruled out. True purpura is a condition in which there are extravasations of blood into the

surrounding tissues as a result of some disturbance or defect of the blood clotting mechanism. In acute arteritis there is a definite picture of an infection, with leucocytosis; the blood platelets and clotting time are normal. Syphilis can be ruled out because of the fact that in these cases there is a septic condition, as well as by the absence of a history of lues and by serological study.

CONCLUSIONS.

1. There is an infection of the arteries independent of the general maladies which may be associated with bacteremias.

2. It is an acute condition with a definite clinical picture.

3. According to reported findings in the literature it is presumably caused by some strain of streptococcus, and the point of entrance may be the throat.

4. The lesions in the vessels are varied. The media is most commonly involved. The intima and adventitia, as well as the perivascular tissues, likewise show evidences of inflammation.

5. Diagnoses such as purpura and gangrene should be questioned until all definite conditions can be excluded.

6. There may be hematuria and albuminuria.

7. The clinical picture in the early stage is vague and indefinite so far as a diagnosis is concerned, although it is quite evident that the patient is seriously ill. Later as the bloodvessels become more definitely involved, through the direct action of the bacteria or their toxins upon the arteries, thrombi are produced with occlusion of the lumen of the vessels or rupture of their walls, and the clinical aspect becomes clearer. These developments may be manifested by intense pain, socalled purpuric extravasations of blood, and gangrene. Diagnoses of purpura and gangrene are then likely to be made—vague terms which should be discouraged, since they fail to give any indication of the underlying pathological condition or its etiology.

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8. Usually the extremities, both upper and lower, are affected. The larger vessels may be involved as well as the medium sized and smaller ones, although the latter commonly show the more marked changes.

9. The condition may terminate fatally within a few days or the patient may gradually recover with sloughing of the gangrenous areas, or after surgical intervention.

10. The future of the patients who recover is problematical. It seems hardly possible that an infection of such delicate structures can subside without leaving some permanent damage. It will be interesting to follow up such cases and to see whether at some future time there may not develop circulatory disturbances with symptoms and trophic changes not unlike those seen in Buerger's disease, or perhaps endocardial or other inflammations of embolic origin.

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2035 CHESTNUT STREET.

PITUITARY DISORDERS IN THEIR RELATION TO ACROMEGALY (HYPER-PRE-PITUITARISM), WITH SUGGESTIONS FOR THE USE OF A MORE PRECISE TERMINOLOGY

By E. B. KRUMBHAAR, M.D., PH. D.

Director of the Laboratories of the Phila. Gen. Hosp., Assoc. Prof. of Pathology, U. of P. Grad. School of Med.

(From the Laboratory of Post Morten Pathology of the Phila. Gen. Hosp.)
READ BEFORE THE PHILADELPHIA PHYSIOLOGICAL SOCIETY, JAN. 16, 1922.

Diseases of the pituitary gland possess a peculiar interest not only for the internist or ophthalmologist and neurologist, on account of the character of the symptons produced, and for the surgeon on account of the problems of operative intervention, but also to the physiologist and "dynamic pathologist" concerned with the relation of this structure to general body functions in health and disease. In fact, our present knowledge of the pituitary has perhaps been chiefly advanced by the clinical study of cases of disordered function, a belief which has made me think it worth while to present the accompanying series of cases. Since the appearance of *Cushing's* masterly monograph 10 years ago, but little practical progress has been made, so that we have not yet fulfilled his prophecy that "we are unquestionably approaching a stage in our knowledge when the classification or grouping of the cases here employed as a provisional basis for clinical use, will no longer be necessary." For instance,

in the most recent consideration of this topic,[1] the pituitary is not once considered as other than a single gland, a failure that would be much less apt to occur if a more precise terminology were in vogue. Before discussing cases in detail, therefore, I would like to make a plea for the use of more specific terms that we have found useful in our discussions in these laboratories.

The pars intermedia and the pars neuralis are, though anatomically distinct, considered today with propriety from a functional point of view as the "posterior lobe." It is therefore obvious that disturbances of pituitary function may be grouped under 5 heads: 1, overfunction of the anterior lobe, 2, underfunction of the anterior lobe, 3, overfunction of the posterior lobe, 4, underfunction of the posterior lobe, 5, perverted function of one or both lobes. In spite of this obvious state of affairs it is still customary (perhaps on account of the unavoidable length of more precise terms) to use the older terms hyper, hypo, and dyspituitarism. This lack of precision places such a handicap on the intelligent discussion of the nature of disorders of pituitary function and of given endocrine cases, that I venture to recommend the use of more precise, though clumsier terms. If "hypophysis" and "pituitary" were not so firmly established as synonyms, one might take advantage of their etymological derivations to designate the first 2 classes as hyper- and hypo-pituitarism, and the next 2 as hyper- and hypo-hypophysiasm, disregarding the fact that the p. intermedia probably has an ectodermal origin.

With the addition of an extra syllable, however, we may use: (1) hyper-pre-pituitarism; (2) hypo-pre-pituitarism; (3) hyper-post-pituitarism; (4) hypo-post-pituitarism; (5) dyspituitarism.

1. As hyper-pre-pituitarism are considered such growth changes as giantism and acromegaly which are commonly associated with hyperplasia or adenoma of the acidophile cells of the anterior lobe.

2. Hypo-post-pituitarism is manifested, in the present state of our knowledge at least, by dwarfism. There are but few definite clinical observations to support this view, but it is probable this deficiency is a factor in many cases of dwarfism. The possibility of such a lesion is well demonstrated by a recent finding in these laboratories of almost complete loss of the anterior lobe. (Fig. 17)

3. Hyper-post-pituitarism is likewise a rather hazily understood

[1] Hutinel, V. Mailleot, Dystrophies Glandulaires et Mono Symptomatiques, Annales de Med. '21, X. 100.

condition. Lessened sugar tolerance, increased basal metabolism and other antitheses of the 4th class might logically be included here and in fact have been so placed in a few instances.

4. Hypo-post-pituitarism includes a large and better known group of disorders such as are prominent in *Fröhlich's* syndrome and similar disturbances of metabolism, cardio-renal-vascular regulation and sexual characteristics.

5. Under dyspituitarism should be grouped following *Cushing's* suggestion, mixed or transition cases, i.e., any perversions of the functions already referred to or those cases which have not shown a preponderance of symptoms attributable to any one lobe. Here also must be placed cases that have progressed from one of the first four groups to a composite mixture of symptoms referable to hyper- or hypo-function of both lobes, as *Cushing* has demonstrated to be so frequently the case in acromegaly. In using such terminology it must also be borne in mind that the relation of certain clinical factors of considerable importance, such as "neighborhood" or distant cerebral symptoms and of the other glands of internal secretion have been left out of consideration.

To return to the relation of pituitary tumors to acromegaly let it suffice here to recall a few prominent landmarks:

1. Their frequent association, which was firmly established by clinico-pathological evidence within a few years of Marie's[2] original description of this striking clinical condition in 1882. 2. *Massalongo's*[3] and *Tamburini's*[4] hypothesis that acromegaly is due to a hyperfunction of the anterior lobe (hyper-pre-pituitarism); with *Massalongo's* corollary that giantism results if the epiphyses are not yet ossified, this is now the most widely accepted view. 3. *Benda's*[5] demonstration that increase of the acidophile cells of the anterior lobe was probably the important factor in producing hyperfunction; 4, the discovery of various accessory hypophyses (a, hypophysis accessoria cranii; b, h. a. canalis craniopharyngea; c, h. a. pharyngea); 5, and by *Erdheim's*[6] demonstration of an acromegalic with a normal hypophysis but with an acidophile adenoma of the pharyn-

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[2] Marie. P., Revue de Med., 1886, VI, 297.
[3] Massalongo, R., Riforma Med., 1892, VIII, 74, 871.
[4] Tamburini, A., Riv. Sper. di freniat., 1894, XX, 559.
[5] Benda. C., Berl. Klin. Woch., 1900, XXXVII, 1205.
[6] Erdheim, J., Franf. Zeitsch. of Pathol., 1910, IV, 70.

geal hypophysis. The arguments for and against the hyperfunction conception of acromegaly are to be found in *Cushing's* book (page 250 et seq.). In view of *Erdheim's* discovery, however, it seems only proper to throw out of count all cases of acromegaly with normal pituitaries in which the accessory hypophyses have not also been most carefully studied. In cases of acromegaly with non-acidophilic tumors of the pituitary the possibility of a progression beyond the acidophile stage must also be borne in mind. Even when many of the so-called exceptions to the hyperpituitarism theory are put in the suspicious class by such means, however, it must be recognized that other valid exceptions still exist, and will probably increase in number. *Bailey*[7] has recently supported this view with the cases of *Cagnetto, Zak. Kraus* and others (acidophilic increase without acromegaly) and with *Yamada's* case of acromegaly without pathological change in the pituitary. I cannot see, however, that adequate evidence has been produced to support the view that the hyperplasia, when present, is secondary to some biochemical disturbance.

Case 1—(P.G.H. Autopsy No. 5645). Chronic Acromegaly. No signs or symptoms of cranial disturbance. Death from tuberculous pericarditis and cardiac failure. At autopsy—acidophile adenoma of anterior lobe of pituitary.

History—J. D., negro, 43, laborer, admitted to the service of Dr. Riesman in the Philadelphia General Hospital on October 25, 1920, suffering from shortness of breath and other signs of marked cardiac decompensation.

The diagnosis of acromegaly was made by one of the staff as he saw the patient arrive in a taxicab. No change in his appearance noticeable either to himself or his friends, had occurred in at least the past 21 years. Photographs or details of size of hands and feet were unfortunately not available.

For three months he had been suffering from shortness of breath on exertion and evening edema of ankles and feet. Before that time he had successfully labored in a meat-packing establishment carrying heavy cases of ice and boxes. He was usually called on to do the hardest lifting on account of his great strength. Three months before admission he weighed 248 pounds.

[7] Bailey, P., Jour. Med. Research, 1921, XLII, 349.

Except for gonorrhea at 18, and a chancre at 23, he had always been healthy and strong, and had never taken a dose of medicine until his present illness. Was never married. Was a heavy whisky drinker and user of tobacco.

His father, who died at 63 of heart trouble, was said to have been a very large man and to have had a large head and hands. Other family history negative.

Examination:—Showed a middle aged, colored "giant" (as he was 5′ 9″ tall, this must have referred to his great muscular development). Head "diamond" shaped, greatest circumference 25″.

Fig. 1.—Case 1. Showing large jaw and prominent soft tissues of nose and mouth.

Occipito-mental 12″, occipito-frontal 10″. Face covered with short, kinky, gray-black hair; hair normal; eyeballs prominent. Pupils and eyesight normal. Tongue very large. Teeth in fair condition, spacing between teeth of upper row. Hands 8½″ long and very broad; feet 11½″ long, very broad with short, stubby toes. Heart dullness increased, action arrythmic, with mitral systolic murmur, weak muscle sounds and roughened second aortic. Lungs: signs masked by loud bubbling râles. Death from pulmonary edema.

Clinical Diagnosis:—Acromegaly, acute myocarditis with decompensation, pulmonary edema.

Autopsy:—(Drs. B. Crawford and N. Winkleman.)

Skull unusually thick, especially in the frontal and occipital region, in one area measuring 2 cm. in diameter. The dura was normal; the pia only slightly injected and presented no peculiarities. The brain itself was of fairly good size and weighed 1,350 gms. It was not edematous. On removal of the brain it was noted that there
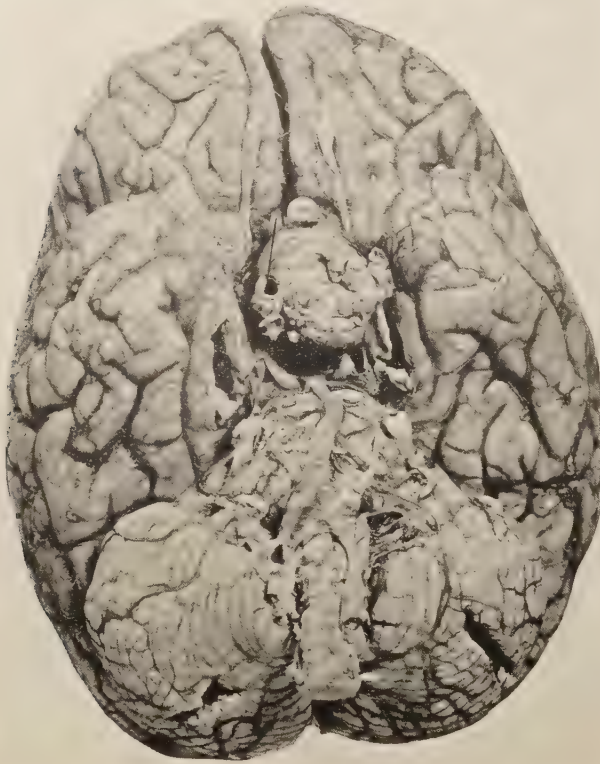
Fig. 2—Case 1. Base of brain showing acidophile adenoma of pituitary.

was a large tumor of the pituitary region which pulled the optic nerves taut and when this tumor was lifted up with the pituitary, the fossa was found to be very much deepened and widened and the tumor adherent to the surrounding periosteum and difficult to separate from it. At the anterior angle of the tumor a part of the mass had broken through the capsule which surrounded it and presented as

a small mulberry mass about the size of a pea. At the lower surface of the tumor there was a fairly definite cyst which ruptured on removal and extruded a semi-fluid gelatinoid material. The pituitary and tumor were removed en masse with the surrounding bone of the sella turcica. The tumor itself was about the size of a small lemon, soft, with a definite capsule, and on its upper surface the pituitary
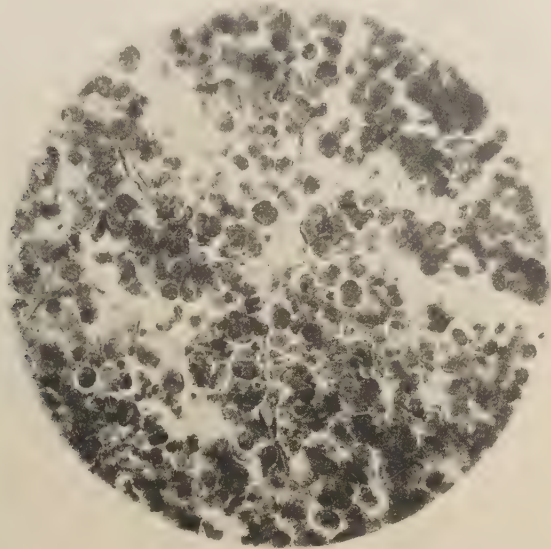
FIG. 3.—Case 1. Photomicrograph of adenoma, showing uniform type of cell, small nucleus, much protoplasm, containing acidophile granules. Note absence of normal acinous arrangement of blood vessels.

gland presented as a small flattened ribbon-like affair that was difficult to differentiate from the tumor mass. The optic chiasm was flattened out and extended back to the corpora mammillaria which was crowded posteriorly and also flattened. The tumor was vascular.

On histological examination this tumor was seen to be composed almost entirely of cells closely resembling the typical acidophile cells of the anterior lobe. The arrangement in acini was very imperfect and connective tissue stroma very scanty. Blood vessels were reduced in number and only moderately filled with blood corpuscles. The generous protoplasm of the acidophile cells was packed with coarse acidophile granules, the small compact nucleus being eccentrically placed. They varied considerably in size. Less than 1%

were basophile and chromophobe cells, the latter being the more numerous. The mulberry-like mass presented a similar histological appearance without evidences of malignancy. A small remnant of the anterior lobe was found compressed between the adenoma and the pars intermedia.

Fig. 4.—Case 2. Showing separation of teeth of lower jaw.

The other pathological findings were chronic obliterative tuberculous pericarditis, with cardiac hypertrophy and dilation; lobular pneumonia with gangrene of the left lower lobe; chronic fibrous tuberculosis of.lungs and lymphnodes, and chronic fibrous pleurisy.

Case 2—(P.G.H. Autopsy No. 6286). Very early acromegaly, diagnosed clinically by recent clubbing of fingers and separation of lower teeth, with suggestive facies. No symptoms of cranial disturbance. Death from pneumonia and lung abscess. At autopsy, hyperplastic pituitary, chiefly due to acidophile cells of anterior lobe.

History:—E. F., white, 43, janitor, admitted to the service of Dr. Sailer in the Philadelphia General Hospital on September 30, 1921, suffering from cough, dyspnea and blood spitting.

Beginning acromegaly was suspected by Dr. Sailer on account of the patient's facies and markedly clubbed fingers and the diagnosis strengthened by the fact that the patient's lower teeth were considerably separated and that the spaces had only begun recently to

Fig. 5.—Case 2.   Showing clubbing of fingers.

increase. Unfortunately the patient's pulmonary condition was too extreme to permit proper pituitary tests. Neither he nor his friends had noticed any changes in his appearance other than those mentioned.

The patient had been a motorman until he had a bad attack of influenza in 1917, from which he never recovered. Had only been able to do the lightest janitor's work for 2 years, suffering from a bad cough with copious expectoration, loss of weight and evening rises of temperature. For a week before admission these symptoms had been worse, with blood-tinged sputum.

He had had scarlet fever and otitis media at 16. Habits irregular, but denied venereal disease. His mother died of influenza in 1917 and one brother of "galloping consumption."
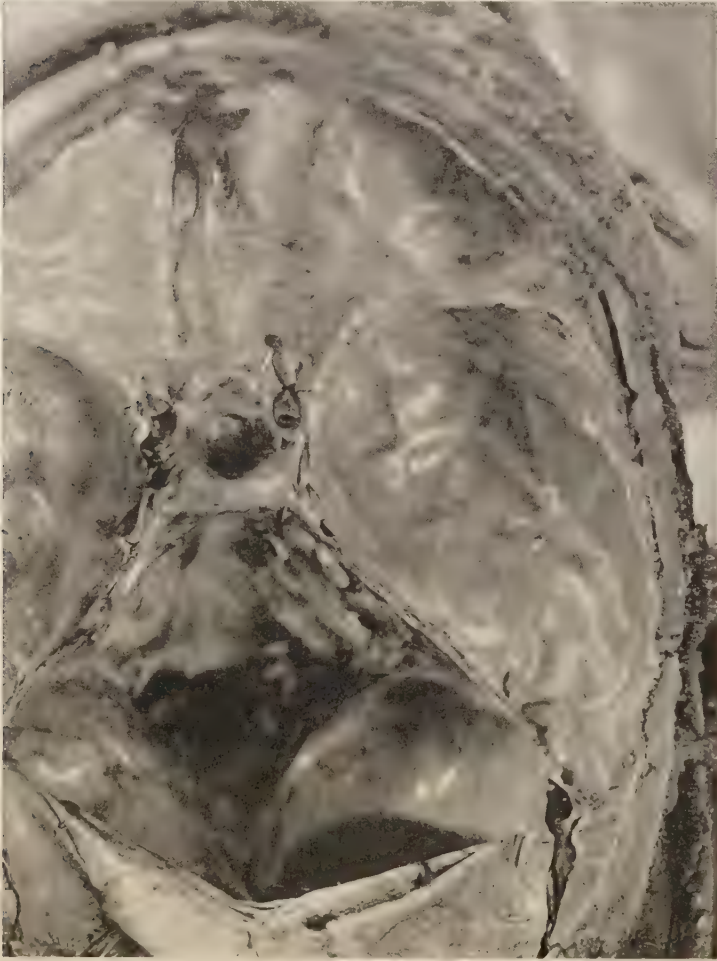
Fig. 6.—Case 2. Base of skull, with enlarged, deepened pituitary fossa.

Examination:—Patient prefers sitting posture and is very dyspnœic. Pupils irregular but react promptly to light and accommodation. No disturbance of vision. Hair normal. Teeth in bad shape,

and lower teeth widely apart. Tongue normal. Thyroid not palpable. Fingers short and fat, with marked clubbing of tips. Toes also clubbed. The lungs showed signs of consolidation of left base and impairment of left apex. The heart was enlarged with a systolic murmur transmitted to the axilla. The electrocardiogram
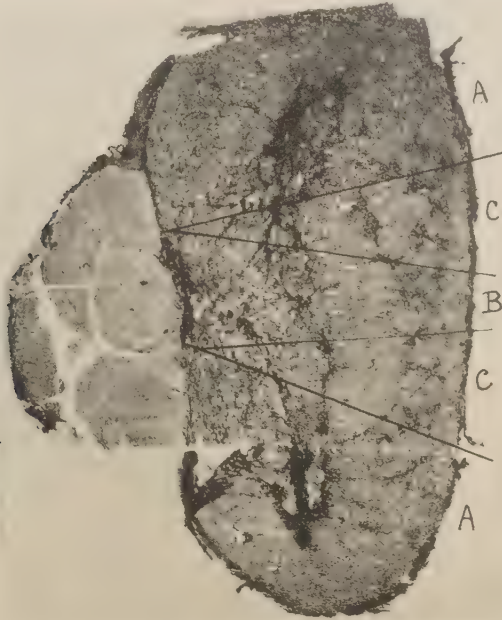
FIG. 7.—Case 2. Transverse section of pituitary, showing hyperplasia due chiefly to acidophiles. Areas of the 3 types of cells: (a) acidophiles greatly predominant; (b) basophiles numerous; (c) chromophobe cells [degenerated chromophiles (?)] predominant.

showed left ventricular preponderance. Leucocytes 34,400, polys 82%, lymphocytes 17%, mononuclears 1%, R.B.C. 5,120,000. Wassermann 4 plus in all antigens. Blood pressure 110—70. Urine: heavy trace of albumin, hyaline casts. In spite of digitalis and neoarsphenamine the patient grew steadily weaker and died from pulmonary edema.

Clinical Diagnosis:—Beginning acromegaly, lobar pneumonia, chronic mitral endocarditis and nephritis, syphilis, pulmonary edema.

Autopsy:—(Drs. Weiss and Patfen.) Meninges normal except for pial thickening of interpeduncular space. Skull normal. Brain weighs 1,475 gms. and is apparently normal. The pituitary body, cupped on the superior surface, is distinctly enlarged, measuring 17x12x7 cm. The post lobe is of normal size, and the infundibulum is normal but somewhat to the left of the midline. The sella
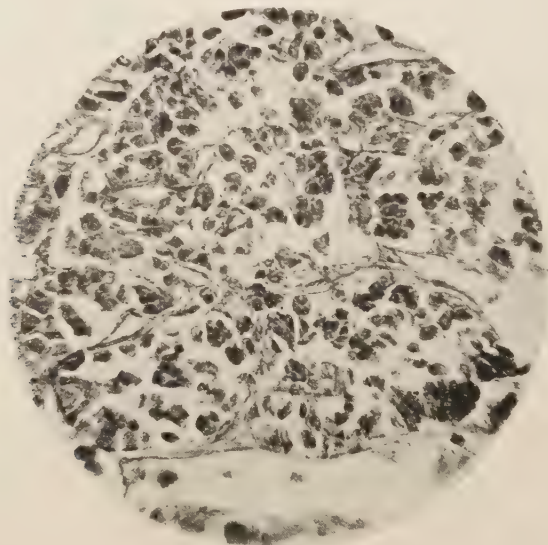
Fig. 8.—Case 2. High power of area A. All the larger cells and many of the smaller are acidophiles, the remainder chromophobes.

turcica is unusually deep, with a normal floor, and slight hypertrophy of the postclinoid processes.

On *histological examination* the acidophile cells are found to be greatly predominating in almost one-half (20 out of 45 low power fields) of a transverse section of the anterior lobe. This predominance is especially marked in symmetrical postero-lateral areas of the anterior lobe (see Fig. 7) but is not limited by a connective tissue framework that extends fanwise from the pars intermedia. In these areas acidophiles were computed to comprise 83.7%; basophiles 3.4%; chromophobe cells 12.9%. In a mesial belt of the same section (occupying 7 of 45 lower fields) basophiles are much more prominent, though acidophiles and chromophobes are still to be

found in considerable numbers (acidophiles 16.9% ; basophiles 53.6% ; chromophobe cells 29.5%). The basophiles showed a slight tendency to vacuolization. In the intermediate areas chromophobe cells are more numerous. Many of these, however, are large cells with all the characteristics of a chromophile cell except the granules, so that it seems probable that they are altered or degenerated cells of the acidophile or basophile type. A differential count· in these
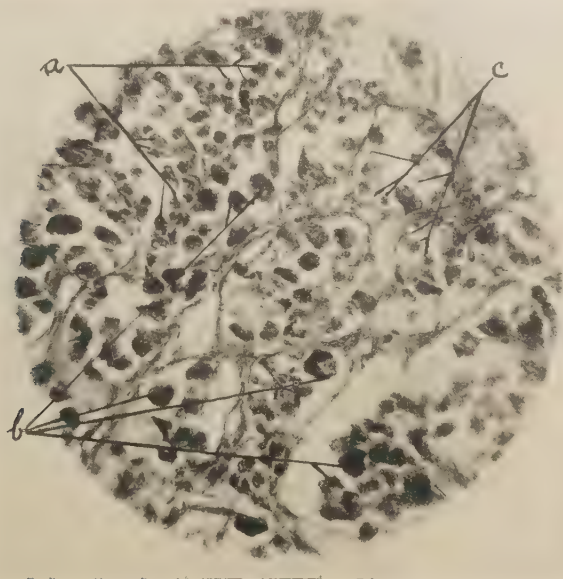
Fig. 9.—Case 2. Area B (*a*) acidophiles; ·(*b*) basophiles; (*c*)chromophobes.

regions reveals: acidophiles 7.5% ; basophiles 13% ; large chromophobes (?) 30% ; small chromophobes 49.5%. It is, therefore, obvious that not only is the anterior lobe considerably increased in size but that the proportion of acidophiles within the lobe is also considerably increased· above normal.

The following body measurements are pertinent: Length 170 cm., weight 190 lbs. ; circumference of head 60 cm. ; length of nose 7 cm. ; torso—leg ratio 45.6x96.2 cm. ; length of arm 36, of forearm 30 ; of hand 21 ; of middle fingers 15 ; circumference of hand 22.5 ; length of thigh 42.5 ; of leg 45 ; of foot 26 ; circumference of foot 25 cm.

The other pathological findings were: pulmonary abscess of left upper lobe with bilateral supperative pneumonia, chronic mitral and aortic endocarditis.

CASE 3:—(Pa. Hospital Autopsy No. 1759.) Acromegaly of 2 years' standing, failing vision of right eye for one month. Headache 2 weeks. Cause of death not ascertained (cerebral pressure ?).

FIG. 10.—Case 2. Area C, lettering as in Fig. 9.

At Autopsy, degeneration cyst of pituitary, with remnants of adenocarcinoma (?) of anterior lobe in cyst wall.

History:—C. V., white, 23, butcher, admitted to the service of Dr. Newlin in the Pennsylvania Hospital, October, 1914, on account of headache. The diagnosis of acromegaly had been made on a previous admission in 1912. The onset of the disease was first noticed 2 years previously when his hands were found to be getting larger. Shortly after his feet began to enlarge, with a change in the size of his shoes from 7½ in 1911, to 11½ in 1914. He had constant headache for 2 weeks before admission for the first time since his sick-

ness began. One month before, he noticed that sight in his right eye was failing. Vision of left eye and hearing normal.

In 1913, when he was admitted complaining only of pain in his left leg, the peculiar development was noted as being more marked in the soft parts than under the X-ray. The sella turcica was found to be ½ larger than normal and the postclinoid processes almost

Fig. 11.—Case 3. Cyst wall with infiltrated carcinomatous tissue.

destroyed. Eyes reported normal except for an external strabismus of the right (Shoemaker). His past history and family history were negative.

Examination:—Gigantic in size and development (183 cm. tall). Head abnormally large (59 cm. in circumference). Eyes divergent, fixes with left eye, ocular movements ful   Right eye blind, no light perception; left eye shows temporal h mianopsia. The jaw is

large and the distance from the nose to the tip of the chin increased. The upper teeth show some spacing, the lower teeth do not. Hair of scalp and body normal. Ears, nose, tongue and mouth very large. Does not appear to be mentally acute. Enlargement of upper extremity involving distal ends of radius and ulna. Hands large and spade-like, with thickening of finger pads, but have not lost their symmetry. Grip weak. Feet tremendously enlarged (30.5 cm. long). Wassermann negative.

At Autopsy:—(Dr. Samuel.) The skull was found to be relatively thinner than the other bones. The sella turcica was broadened and thickened. The pituitary was replaced by a cyst under tension, measuring 4x6x3 cm. in diameter. The walls were very thin and translucent, with evidence of a thin, compressed layer of glandular tissue on one side. The optic chasm was stretched over the belly of the cyst.

Histological examination of this area showed atypical acinous epithelial cells with large nuclei, varying considerably in size and in a few instances undergoing mitosis. They were not enclosed in acini but interspersed with varying amounts of connective tissue that produced not infrequently an effect of clumping. This connective tissue was both of a sparse cellular and dense fibrous type. The wall of the cyst was not lined with cells. A few other microscopic cysts were also found.

The autopsy also disclosed a marked congestion of the abdominal viscera. The thyroid, thymus, adrenals and pancreas were normal. The testicles showed an increased amount of connective tissue between the lobules. An acute interstitial nephritis was apparently the cause of death.

CASE 4:—(Pa. Hospital Autopsy No. 1126, Bulletin Ayer Clinical Laboratory, Philadelphia, 1908, No. 5, p. 32.) No signs of acromegaly or other disorders of pituitary function. Signs of intracranial pressure for 6 months. Death from acute endocarditis and bronchopneumonia. At autopsy a chromophobe adenoma of the anterior lobe of the pituitary, with preservation of the compressed anterior and posterior lobes.

History:—W. B., 43, negro, laborer, admitted to Pennsylvania Hospital, August 11, 1908, during the service of Dr. Newlin. His

family history was negative. He was born in the eighth month of pregnancy and was weak till he was 10 or 12 years old. He had temporary lateral curvature of the spine which he outgrew. At 18 he was strong and healthy. He always worked at hard manual labor. His wife, married ten years ago, says he was as corpulent

Fig. 12.—Case 4. Base of brain, showing chromophobe adenoma of pituitary.

and strong then as at present. She had one abortion in the seventh month of pregnancy, and had one child which lived only a few hours. Veneral history was denied. Sexual habits normal. The patient always drank to excess and smoked tobacco. "He always seemed to suffer in the top part of his head" and has always had headaches

since a small boy. These have been worse since his skull was fractured (?) by a blow from an iron gate, three years ago.

Last winter he first noticed attacks of dizziness, nausea, vomiting and increased headache. The sight of both eyes began to get dim. Lately the attacks have come about once a week. On the day of his admission he had an attack in which he was unable to stand upright or to speak, though he was conscious and evidently understanding what was said to him. When he arrived in the patrol wagon he was unconscious and limp. Later he became stiff all over and died two hours after admission without regaining consciousness. The urine contained albumin. No physical examination made.

At Autopsy:—(Dr. Krumbhaar.) The following measurements were taken: The body weighs 195 lbs., and measures 175 cm. in length; circumference of head, 57.5 cm.; from symphysis of chin to angle of jaw, 12 cm.; chest 108.5 cm.; abdomen 98.5 cm.; from top of sternum to symphysis of pubis 58 cm.; from tip of acromion to styloid process of radius 62 cm.; circumference of arm 35 cm.; of forearm 30 cm.; from styloid process of ulna to tip of forefinger 19 cm.; from great trochanter to internal malleolus 88 cm.; circumference of thigh 59 cm., of calf 38 cm.; length of foot 27.5 cm.

Brain: On removing the calvarium, which is normal and not thickened and shows no signs of fracture, the meninges appear normal and the brain tissue somewhat soggy. The lateral ventricles are distended with fluid. Weight of brain 1,240 gms. The pituitary fossa is found to be much enlarged and to be filled with a humor-like mass about the size of a crab-apple. The fossa is shallow and has a much wider diameter than normal. The posterior clinoid processes are obliterated.

The tumor occupying the sella turcica is reddish-gray, soft and almost fluctuating. It shows some dark red areas and dilated vessels. On section it is found to have a similar hemisphere (about twice the size of the other) which projects up into the right frontal lobe. On its anterior surface is a smaller lobule the size of a cherry. The two hemispheres are constricted about the middle by the optic chiasm anteriorly and by the optic tracts posteriorly. Until the pia was dissected only the half below this constricting girdle was visible. The cut section of this tumor mass bulges, is moist and of a reddish flesh color. The optic chiasm and tracts are much stretched and

attenuated by pressure from the tumor. On separating the loose connective tissue which joins them to the tumor, it can be lifted out of its socket except for a long, thin, delicate pedicle joining it to the base of the brain.

Sections from all parts of this tumor show a very cellular tissue that varies but little in different parts. Remnants of both portions
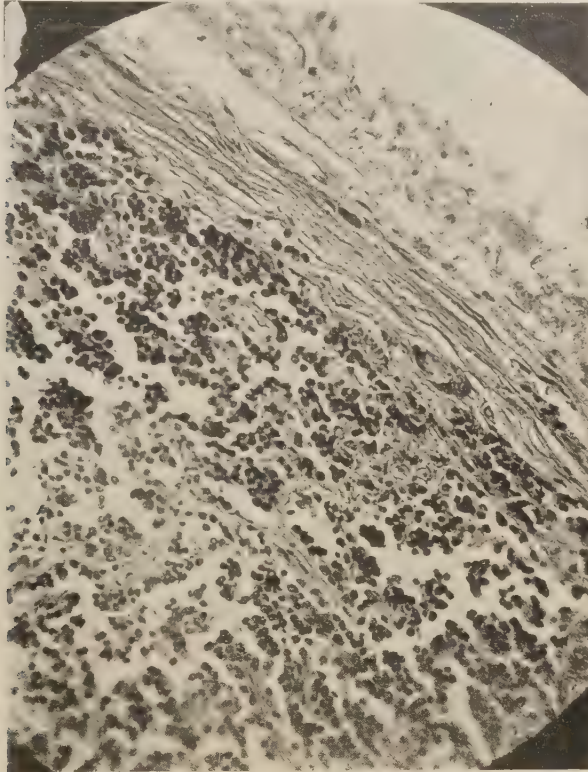
FIG. 13.—Case 4. Encapsulated adenoma, composed of small chromophobe cells.

of the normal gland are found stretched about it like an envelope, with columns of compressed cells in the anterior lobe. The tumor is bounded by a fairly thick, regular capsule which in no place appears to be infiltrated by the cells of the mass of the tissue. The tumor cells have a small round, highly chromatic nucleus and either no visible protoplasm or considerable homogeneous protoplasm, the

latter appearing not unlike a plasma cell. Nothing approaching chromophile granules is demonstrable by ordinary or special stains. Frozen sections and teased specimens show th esame character of cell. The interstitial tissue is very scanty for the most part showing as extremely fine, delicate blue fibres (Mallory's stain) or occasionally short sections of fairly small trabeculæ. Special stains for neuroglia fibres (Weigert and Mallory), myelin sheaths (Weigert) and elastic fibres (Verhoeff's) fail to show their presence. Small capillaries are fairly numerous in some sections (especially those from the superior and posterior portions) but are very sparse in other parts. A very few larger vessels are found in the tissue, but even in these only a few scattered elastic fibres can be found.

In addition the autopsy showed an acute vegetative mitral endocarditis, lobular pneumonia, marked congestion of viscera, chronic mitral and aortic endocarditis with cardiac hypertrophy, chronic pleurisy and arteriosclerosis. The other glands of internal secretion were normal, except for a marked congestion of the parathyroids and localized areas of fibrosis in the testicles which were equalled by sclerotic changes in other organs.

CASE 5:—(Philadelphia Gen. Hosp. Autopsy No. 6048.) Failing vision beginning 3 years ago and progressing to total blindness with coincident signs of hypo-post-pituitarism. No relief from decompression operation. Cause of death, brain tumor. At autopsy, cyst of pituitary with destruction of both lobes and of optic chiasm. Visceral hypoplasia.

History:—P. J., mulatto, 29, stevedore, admitted to the service of Dr. Lloyd in the Phila. Gen. Hosp., Dec. 12, 1920, complaining of lost vision and headaches. His eyesight began to fail in 1918 after a severe attack of influenza. It got better in the spring of 1919 and he was able to work till April, 1920, when it became so bad that he could not see enough to get around. It grew gradually worse until 2 weeks before admission, when spells of weakness and staggering supervened. He has been subject to frontal headache since he was "beaten up" in a riot 4 years ago, but headaches have been much worse since May, 1920. He states that he has not had an erection for 4 years and had no sexual desire for 2 years. He always feels cold and generally uncomfortable, and has recently had several sudden attacks of projectile vomiting.

He had measles as a child and influenza in 1918. Admits gonorrhea but denies any other venereal disease. He stopped smoking cigars some time ago and never drank. He had eye trouble in 1916, but was greatly improved after his eyes were refracted at the Wills Eye Hospital. His wife and 2 children are healthy; his family history negative.

Examination:—Is well nourished, but the fat distribution is of feminine type, body hair sparse, and external genitalia undeveloped. The left pupil larger than right, laterally oval, and reacts very slightly to light, while the right pupil fails to react. Vision in left eye 1/45, with concentric contraction of visual field. Right eye blind. No extraocular or other motor palsies. Sensation, including taste and smell, not impaired. Reflexes normal, except for absent Achilles jerk. Babinski negative. Hearing and Barany tests normal. Sugar tolerance increased (on 3 occasions 150, 200, and 250 gms. of glucose failed to appear in the urine). X-ray (13309) shows sella turcica greatly enlarged and floor almost entirely destroyed. Urine and Wassermann negative. Hemoglobin 70%; R.B.C. 3,810,-000; Lcts. 9,200; (polys 51%). Blood pressure 96-60.

With a fairly certain diagnosis of pituitary disease a subtemporal decompression was then performed as the more dangerous attempt at extirpation did not seem justifiable with the advanced state of the optic atrophy. This gave only temporary relief, and the administration of pituitary extract proved entirely ineffectual. Some 3 months later he gradually grew weaker, refused nourishment and died with the usual signs of increased intracranial pressure.

At Autopsy:—(Drs. Lucke and Winkelman.) The body measured 165 cm. and weighs 70 k. Bone development normal, but soft parts show a distinct feminine habitus (fat distribution, curved hips and thighs, mammary glands slightly prominent, etc.). Beard and mustache very scanty with downy hair (equalling that of an average boy of 15). Lips fleshy. Skull, hands and feet normal size and shape. External genitalia small.

The brain weighs 1,580 gms. and is lightly edematous. At the base a large greenish mass, 5x9 cm., occupies the pituitary fossa and a deep depression in the cerebrum. A locule 4 cm. in diameter extends in the middle fossa beneath the right temporal lobe. On cutting transversely through the cyst it is found to extend through

the basal ganglia on the right side destroying the greater part of the optic thalamus and invading the internal capsule. The roof of the cyst is a definite wall in the basal ganglia with hardened and brownish discolored tissue beyond. The optic nerves are flattened almost to paper thickness with practically no remnants of the chiasm re-
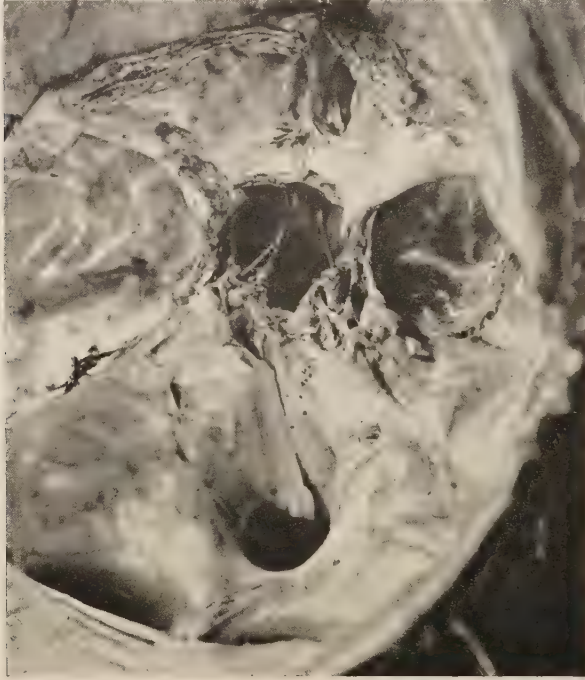
Fig. 15.—Case 5. Base of skull, with enlarged sella turcica communicating with left sphenoidal sinus. Internal carotid arteries indicated by probes.

maining. 80 cc. of brownish cyst fluid had a sp. gr. of 1,027 and contained albumin, 50 mgm. sugar per 100 cc., 590 mgm. chlorides per 100 cc. and many cholesterol crystals, with a positive Liebermann Burchard test for cholesterol. No histological examination was made, as no remnants of the pituitary gland could be found.

The testes are small (3x1½ cm.) and moderately firm. Cut surface shows many pale, fibrous streaks. The adrenals are about ½ their normal size and measure only 2 mm. in diameter. The

yellow outer cortex and brownish inner cortex are equally thin
and the grayish medulla somewhat congested. Microscopically, con-
siderable fatty degeneration. Thyroid normal. Thymus not found.
The aorta hypoplastic (4½ cm. in circumference) but of normal
texture. The heart is pale and small (weight 210 gms.). The
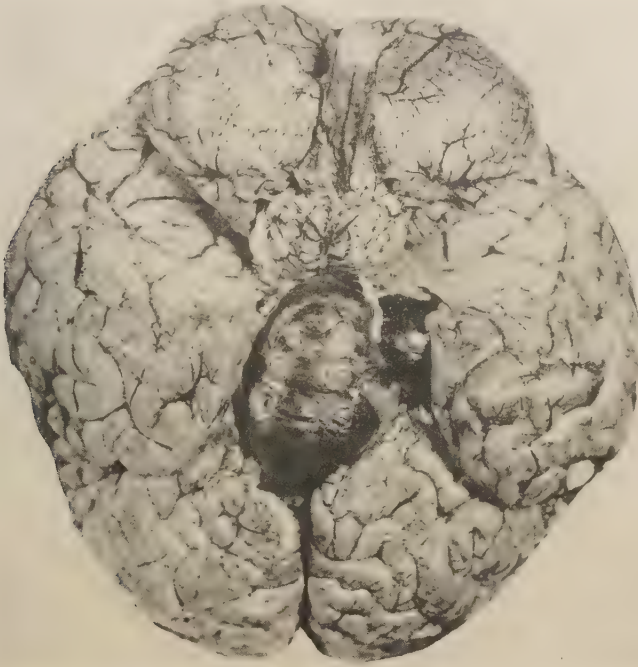
Fig. 16.—Case 5. Base of brain showing large pituitary cyst, with a large
lobule under right temporal lobe. The flattened chiasm constricts the
center of the cyst.

valves normal; the foramen ovale patulous to a small probe. A
mild chronic nephritis and fibrosis of the spleen were also found.

Comment:—Case 1 (J. D.) is a frank case of acromegaly in
which an acidophile adenoma of the anterior lobe was found at
autopsy. It is, therefore, in accord with the theory that an increase
of the acidophiles, representing an increased activity of the an-
terior lobe, is responsible for the development of acromegaly.

CASE 2 (E. F.), which also supports this theory, is of especial interest as an extremely early case of acromegaly, perhaps the earliest recorded that has come to autopsy. The distinct (though not extreme) hyperplasia of the anterior lobe had been sufficient to enlarge the sella turcica, but could not conceivably have exerted any increase of intracranial pressure. It is especially regrettable that time and the patient's condition did not permit a more extensive ante-mortem study to be made. The distribution of acidophile predominance in certain lateral areas of the anterior lobe was also of interest, as were the peculiar large cells with rarefied protoplasm in the anterior regions of the anterior lobe. It was difficult to avoid the impression that these were chromophile cells which for some unexplained reason had lost their granules. It is noteworthy that in some of the lower animals the anterior lobe can be subdivided grossly into similar areas. The occurrence of 83.7% acidophiles in areas representing more than half of a transverse section of a grossly enlarged anterior lobe seems quite sufficient to warrant the diagnosis of acidophile hyperplasia. There is also a reasonable chance that the large chromophobe cells, too, had recently been actively functioning acidophiles. In painstaking differential counts of the hypophysis of the woodchuck, *Rasmussen*[8] found that the acidophiles normally were slightly less numerous than the chromophobe cells, although roughly ten times as numerous as the basophiles. I have not been able to find comparative figures for man, but certainly the proportion of acidophiles is normally much less than in this case. In this connection Lewis'[9] case of acromegaly with a pituitary of normal size but with a great increase of the proportion of acidophiles should also be borne in mind.

CASE 3 (C. V.) is a good example of how a pathological lesion may so progress that the original etiological factor is obscured. Assuming the correctness of the theory above given, the pituitary cyst in this case was probably preceded by an adenoma of the anterior lobe with consequent acromegaly. With carcinomatous degeneration and cyst formation, however, all such evidences were destroyed and if the patient had lived long enough doubtless evi-

[8] Rasmussen, A. T., Endocrinology, 1921, V. 32.
[9] Lewis, D.D., Johns Hopkins Hosp. Bull., 1905, XVI, 157.

dences of hypo-post-pituitarism would have supervened. It is, of course, realized that this interpretation is not capable of proof and that the similarity of the lesions in this and in case 5 might well be emphasized by opponents of this theory.

Cases 4 (W. B.) and 5 (P. J.) are offered by way of contrast as examples of pituitary tumors that do not cause acromegaly. Case 4,
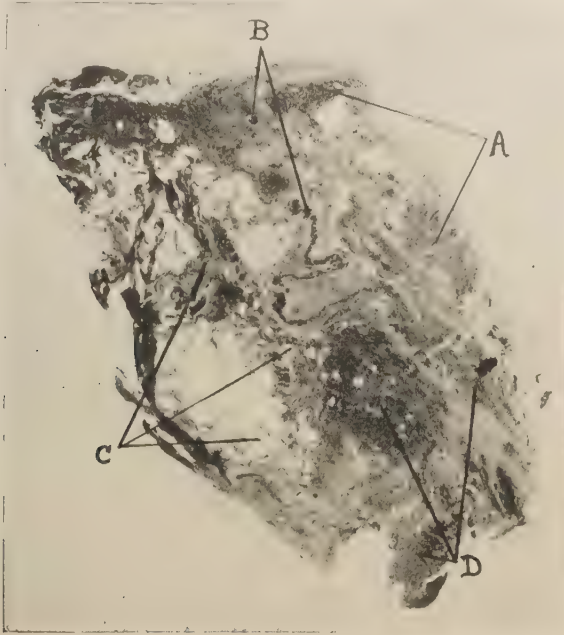
Fig. 17.—Hemorrhage into and fibrosis of both lobes of pituitary with hardly any normal tissue remaining. No symptoms were observed and the condition was discovered by accident at autopsy. *A.* Remnant of acinous tissue of anterior lobe. *B.* Pars intermedia and colloid. *C.* Fibrosed and fatty posterior lobes. *D.* Hemorrhages in both lobes.

a chromophobe adenoma of the anterior lobe, compressing but not destroying the anterior and posterior lobes, is especially useful in bringing out this distinction, as no signs of disordered pituitary function of any kind were to be found or suspected, at least by the methods then in vogue. In Case 5, a large pituitary cyst, signs of hypo-post-pituitarism and of intra-cranial pressure predominated

from the start. With destruction of the anterior lobe one might look also for signs of hypo-pre-pituitarism as well, but here, as in the case illustrated by Fig. 17, such signs were as far as could be told absent for reasons that as yet remain unexplained. The onset of the disorder in adult life would prevent the development of skeletal infantilism, just as pure giantism is found only if hyper-pre-pituitarism occurs before normal skeletal development is finished.
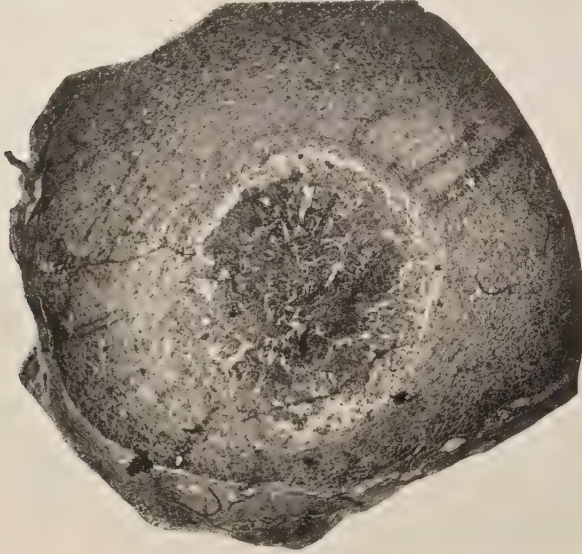
Fig. 14.—Papillary cyst adenoma of pituitary, arising probably from hypo-physeal duct. No symptoms. Discovered accidentally at autopsy.

Conclusions: 1. The theory that acromegaly is due to (or at least follows) hyperfunction of the anterior lobe, after ossification of the epiphyses, as expressed by an increase in acidophile cells, is supported by the cases of this series as well as by the majority of those in the literature.

2. The acidophile increase may be expressed either as a hyper-plasia of the normal lobe (Case 2) or as an adenoma (Case 1).

3. After the development of acromegaly the pituitary lesion may undergo cystic degeneration (Case 3), so that lesions of this nature do not necessarily contradict the above theory.

4. Pituitary tumors may exist for many months even to the extent of destroying both lobes without giving obvious signs of so-called pituitary disease. It is probable, however, that in most, or all, of these cases careful functional tests would reveal a latent disorder.

5. A more precise terminology than that now in use is recommended for the better discussion and elucidation of disturbances in pituitary function.

I wish to thank the several clinicians and pathologists mentioned for their courtesy in allowing this use of their materials.

A SILVER DIFFUSION METHOD FOR STAINING NERVE FIBERS IN PARAFFIN SECTIONS *

WALTER FREEMAN, M.D.

PHILADELPHIA

The method detailed below varies little from that described by Warthin and Starry [1] for the demonstration of spirochetes in paraffin sections. The only modification has been the substitution of a gelatin film for the capillary space between the two coverslips. Warthin and Starry attached paraffin sections to coverslips, washed them in silver nitrate solution, pressed a second coverslip over the section, and allowed silver nitrate solution to diffuse in between the two coverslips.

When their method was used on a suspected gumma of the brain, it was found that numerous fibers were stained, but none of them could be identified as spirochetes. With the idea of determining the possibilities of the stain in regard to nerve fibers, an investigation was undertaken which resulted in obtaining such preparations as are shown in the illustrations.

One difficulty with the Warthin-Starry coverslip method was the uneven character of the silver deposit. This was done away with by embedding the coverslip, face up, in a warm 10 per cent. gelatin solution, allowing it to harden, and then pouring silver nitrate on the surface. The silver nitrate then diffused down to the section. Later the gelatin was melted off and the coverslip immediately immersed in the developing solution exactly as recommended by the authors cited. Even staining, so much desired in all the silver methods was usually obtained.

The method has its limitations. It is not adapted to anatomic work since it does not stain the finest ramifications of the nerve fibers, nor such fibers as occur in the deeper layers of the retina. Due to shrinkage, the finest pericellular networks cannot be brought out in any but perfect preparations. It has advantages over the Bielschowsky frozen section method in that larger sections are used, even the whole cross section of the pons; the tissues are cut thinner, and the relations are maintained. The neurofibrillae are well shown when not altered by disease. Another advantage is that twin preparations can be made with consecutive sections, the one showing the cell processes and neurofibrilae outlined in silver, and the other showing the identical cells stained by Nissl's method to show the tigroid bodies.

1. Warthin, A. S., and Starry, A. C.: Second Improved Method for the Demonstration of Spirochaeta Pallida in the Tissues, J. A. M. A. **76**:234 (Jan. 22) 1921.
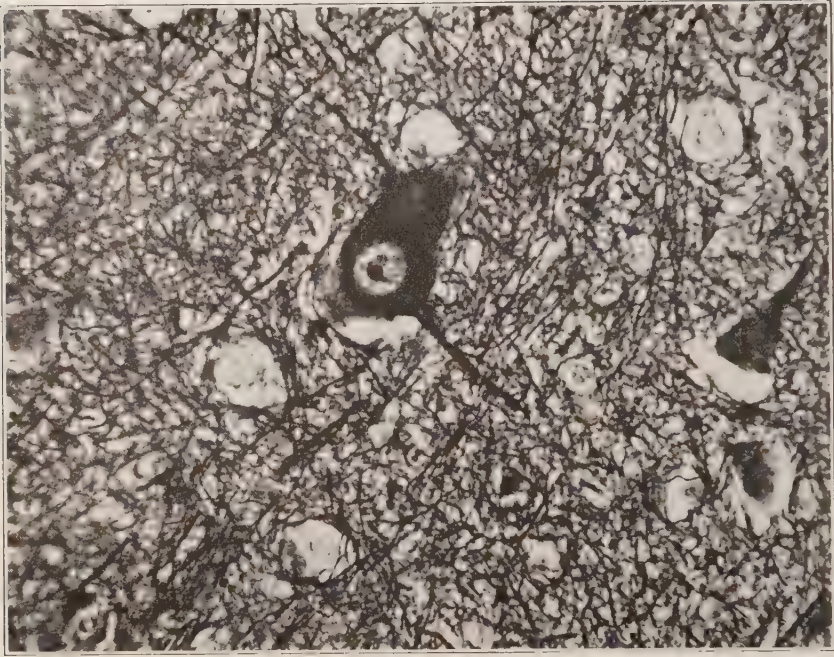
Fig. 1.—Precentral cortex showing Betz cell stained for nerve fibers by silver agar coverslip method.
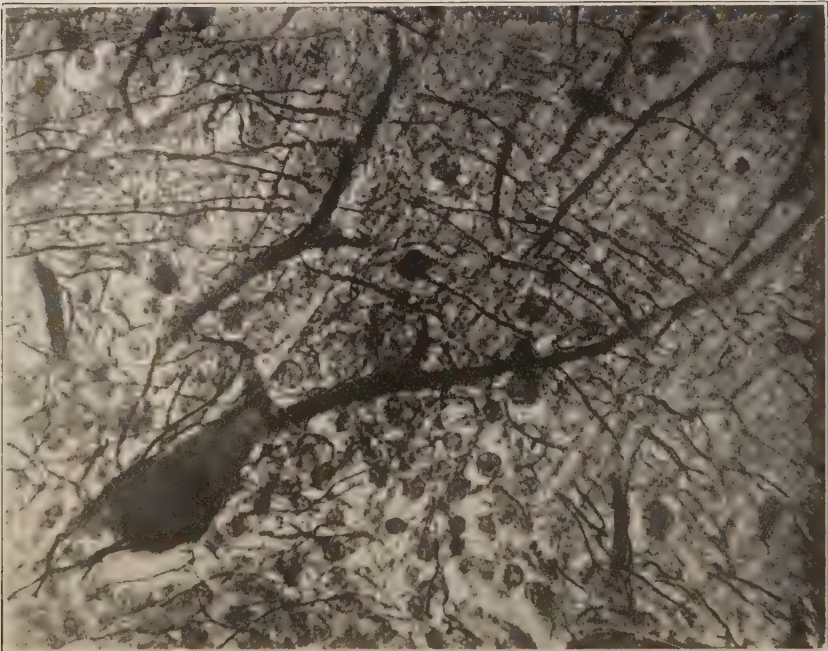
Fig. 2.—Purkinje cell showing basket fibers.

Fig. 3.—Multiple sclerosis; longitudinal section of sclerotic patch stained for axis cylinders.
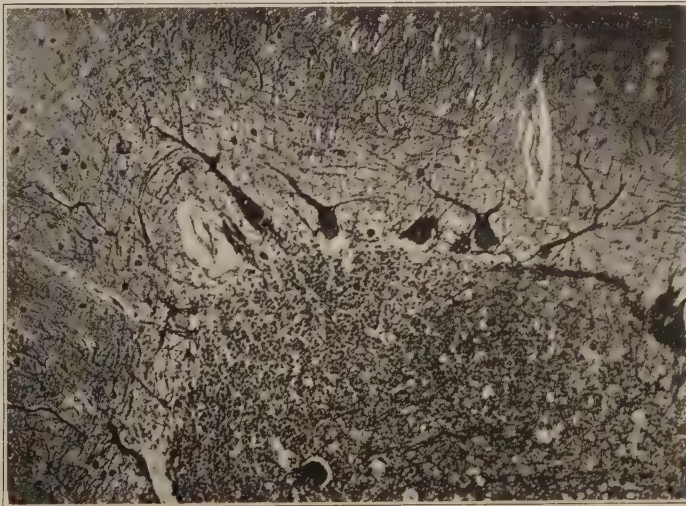
Fig. 4.—Cerebellum; silver diffusion preparation to show nerve cells and processes.

TECHNIC

1. Formaldehyᵈ of alcohol fixation. (Alcohol fixation permits toluidin blue to be used for cell stain with brilliant results.)

2. Paraffin embedding. Cut sections from 5 to 8 microns. These are attached to coverslips which have previously been coated with albumin fixative and dried in the oven over night. They are then blotted and placed in the paraffin oven for from fifteen to thirty minutes.

3. The paraffin is then removed by xylol and the coverslip carried through graded alcohols to water.

4. The coverslip is placed, section side up, in a staining dish the bottom of which is covered by a 5 mm. layer of melted 10 per cent. gelatin, freshly made. The gelatin is allowed to harden and 10 c.c. of 2 per cent. silver nitrate is poured on the surface. This is kept in the dark for twenty-four hours or more. The depth of the gelatin may be increased in order to obtain detail, a longer time being given for diffusion.

5. The gelatin is removed by holding the dish, bottom up, under a hot water tap until the gelatin falls away.

6. The coverslip is plunged without washing into the developer and kept moving until the section is deep brown.

7. It is then washed in water, fixed in 5 per cent. sodium hyposulphite solution, washed again, carried through graded alcohols to xylol and mounted in balsam.

The developer is made as follows:

Glycerin	
Gelatin (10 per cent.)	warm, of each............ 5.0 c.c.
Agar agar (1.5 per cent.)	
Silver nitrate (2 per cent.)............................ 3.0 c.c.
Hydroquinone (5 per cent.)........................... 0.7 c.c.

The glycerin, gelatin and agar agar are added in turn to the silver nitrate, and then the pyrogallol stirred in rapidly. The section is immediately immersed.

All solutions should be fresh and should be made with distilled water. Metal forceps should be coated with paraffin when used in the developer.

An Anatomic Study of the Faisceau De Türck in Relation to the Temporal Lobe

JOHN H. W. RHEIN, M.D.

Professor of Neurology, Graduate School of Medicine, University of
Pennsylvania; Visiting Neuropsychiatrist to the Neuropsychiatric
Ward of the Philadelphia General Hospital

PHILADELPHIA

AN ANATOMIC STUDY OF THE FAISCEAU DE TÜRCK IN RELATION TO THE TEMPORAL LOBE *

JOHN H. W. RHEIN, M.D.

Professor of Neurology, Graduate School of Medicine, University of Pennsylvania; Visiting Neuropsychiatrist to the Neuropsychiatric Ward of the Philadelphia General Hospital

PHILADELPHIA

An opportunity for further study of the anatomic relations of the faisceau de Türck was afforded in a patient who was admitted to the neuropsychiatric wards of the Philadelphia General Hospital in my service on Nov. 30, 1920, and who died on Dec. 10, 1920. The clinical symptoms began six months before the fatal termination, but having no bearing on the anatomic study, will be omitted.

At necropsy examination, a tumor (Fig. 1) measuring 5 cm. anterio-posteriorly and 4 cm. transversely was found occupying the posterior two thirds of the first and second temporal convolutions. It was adherent to the dura, and a cross section showed marked vascularity. Posteriorly the tumor (Fig. 2) did not extend quite to the anterior occipital fissure. Macroscopically, in its posterior aspects, the tumor was rather sharply defined, but there was evidently some invasion of the adjoining cortex and white matter, that is, of the gyrus between the tumor and the anterior occipital fissure, to the extent of about 2.5 cm. Anteriorly, the tumor was less clearly defined except in its outer portion, where for a short distance beneath the cortex it was rather sharply outlined.

Dipping inward, anterior to the tumor, was a fissure which was believed to be the deep temporal fissure, anterior to which was what was regarded as the deep temporal convolution. This convolution macroscopically showed distinct implication by the tumor process. The tumor extended laterally into the brain tissue as far as the inferior longitudinal fasciculus and the optic radiations but did not appear to involve these bundles. Microscopically the tumor proved to be a glioma (Fig. 3).

The brain was cut in serial sections on both sides from the superior level of the tumor as far down as the pons. The tumor itself, with the
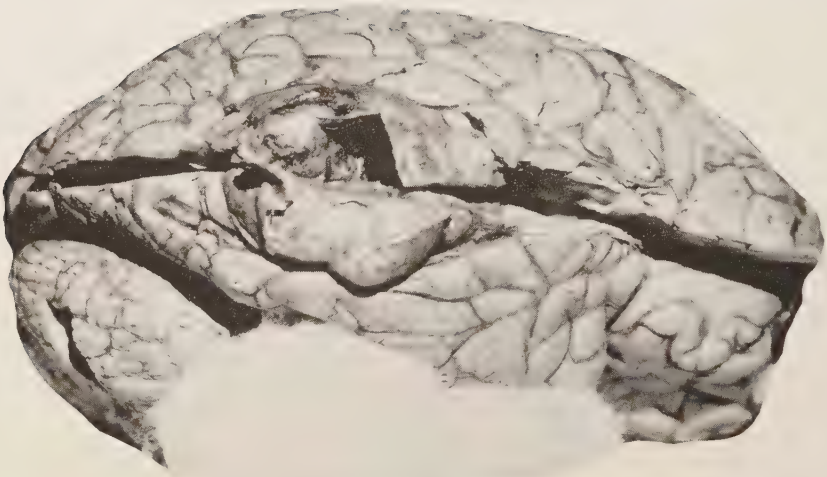
Fig. 1.—Tumor showing its relation to the posterior two thirds of the first and second temporal gyri.
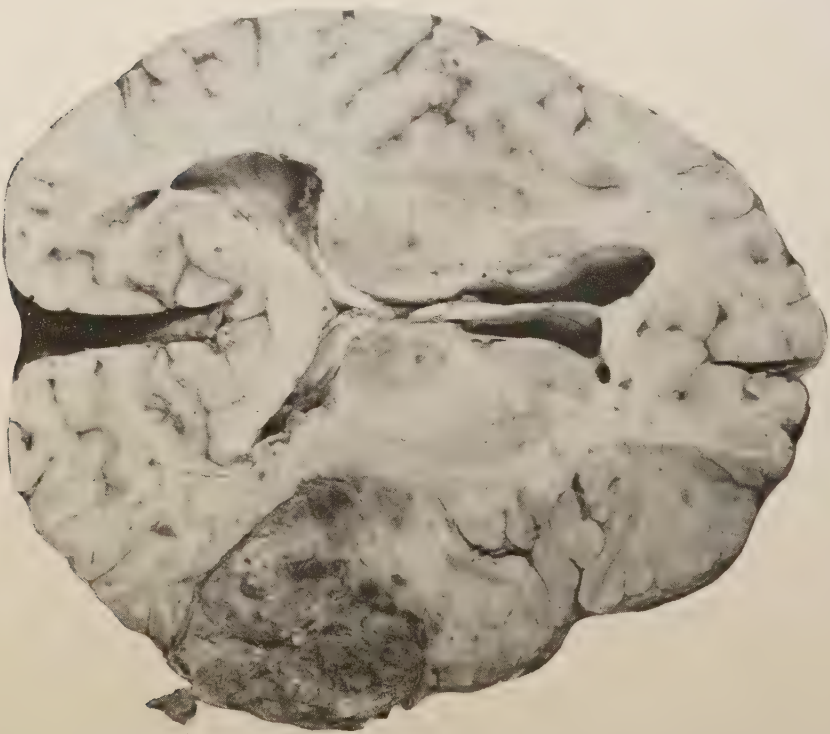
Fig. 2.—Cross-section of the brain showing the extent of the tumor.

adjacent brain tissue, was also cut at various levels in order to study its relation to the adjoining cortex and other brain structures. These sections were stained by the Weigert methods and by hematoxylin and eosin.

The cortex at the site of the tumor was completely destroyed, and nowhere in this region could any cortical tissue or white matter be discovered. The cortical and subcortical layers anterior to the tumor, namely, the deep temporal gyrus which dips normally down almost to the external capsule, the inferior longitudinal fasciculus and the optic radiations were differentiated as to gray and white matter, but in the tissue just adjoining the tumor there was pronounced cellular infiltra-
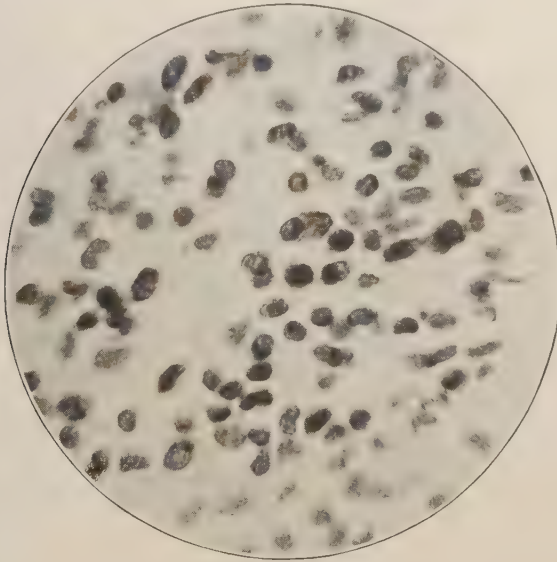
Fig. 3.—Microscopic section of the tumor.

tion with cells having the same characteristics as those found in the tumor.

Posterior to the tumor and between this and the anterior occipital fissure of Wernicke a similar condition could be observed, namely, differentiation of the cortical and white matter and implication of these by the cellular infiltration.

It was possible to conclude from this study that the cortex and white matter of the superior and middle temporal gyri were totally destroyed by the tumor, and the brain tissue anterior and posterior to these regions to the extent of about 2.5 cm. was implicated by a cellular infiltration consisting of cells similar to those found in the tumor proper.

A study of the serial sections of the brain internal to the tumor and the corresponding levels on the opposite side failed to reveal any evidence of degeneration on either side. The faisceau de Türck, at the point where it appears in the retrolenticular region, was intact. The foot of the peduncle stained uniformly and showed an undegenerated faisceau de Türck in this region (Fig. 4).

The duration of the tumor, which showed its first clinical manifestations six months prior to death, justifies the assumption that the degeneration should have had time to appear in the faisceau de Türck, where it appears in the retrolenticular region if not in the foot of the peduncle, if its cortical origin had been destroyed.

In 1912, I [1] read before the American Neurological Association a paper on a study of the faisceau de Türck; and I stated that the

Fig. 4.—Absence of degeneration of the faisceau de Türck.

anatomic relations of the faisceau de Türck were still a matter of dispute. The origin of this tract, according to Déjerine, was the middle portion of the temporal lobe, more especially the cortex of the second and third temporal lobes, which Kann and Brodman believed could be confirmed from their studies. The studies of Kattwinkle and Neumayer placed its origin in the third, second and first temporal convolutions. Flechsig and Van Gehuchten did not agree with this view. Von Bechterew, Flechsig and Meynert and others placed its origin in both the temporal and occipital lobes; Brero, in the parietal lobe; while von Monakow and others asserted that its origin was in the parietal and temporal lobes, von Monakow believing that some of the fibers came from the occipital lobe. Marie and Guillain, from a study of nineteen

1. Rhein, John H. W.: J. Nerv. & Ment. Dis. **38**: No. 9 (Sept.) 1911.

cases, believed that these fibers came from the third temporal convolution. The case of Mills and Spiller, in which the anterior part of the second temporal gyrus and a portion of its upper middle segment were degenerated without showing any involvement of the faisceau de Türck; the case of Löwenstein, in which the anterior half of the second temporal and the anterior two thirds of the temporal were implicated with an intact faisceau de Türck; and a case previously reported by myself in which there was atrophy of the middle portion of the second and third temporal and part of the first temporal convolutions without degeneration of this tract, led me to the conclusion at that time that it could originate only in the posterior part of the temporal gyrus, if at all in the temporal lobes. The case reported in this paper would indicate that the faisceau de Türck does not spring from the posterior two thirds of the superior and middle temporal gyri or the adjacent cortex.

A study of the literature cited demonstrates that the most reliable authorities exclude every portion of the cortex of the temporal convolutions except the posterior part of the inferior temporal gyrus as the origin of this fasciculus. From this, it may be concluded that the faisceau de Türck does not arise from any other portion of the temporal lobe since every other locality may be excluded as a possible origin. I know of no case in literature in which a lesion purely of the posterior portion of the inferior temporal gyrus has occurred and in which studies of the pathology have been made with a view to connecting the faisceau de Türck with this region.

The studies of nineteen cases by Marie and Guillain showed that the region most frequently giving rise to this degeneration is that portion just behind the posterior segment of the internal capsule in the white substance situated between the temporal convolutions and the external wall of the occipital horn of the lateral ventricle, where, they state, the fibers from the third temporal convolution pass. In the second case which I reported in 1912, the findings corresponded to those of Marie and Guillain. In this case, the lesion implicated the white matter of the posterior portion of the posterior segment of the external capsule as well as that of the posterior portion of the temporal lobe and the wall of the descending horn of the lateral ventricle, and the faisceau de Türck was almost completely degenerated. There was a cutting off of the fibers from the third temporal convolution as well as of those from the occipital lobe in part.

I think it may be concluded that if the temporal lobe is the origin of fibers which degenerate in a descending direction, consisting of the faisceau de Türck, they may come from the posterior third of the third temporal convolution.

1732 Pine Street.

TUBEROUS SCLEROSIS *

WALTER FREEMAN, M.D.
PHILADELPHIA

Tuberous sclerosis is a relatively rare developmental anomaly of the brain and other organs, characterized clinically by idiocy and epilepsy, and pathologically by multiple sclerotic nodes over the surface of the brain, multiple subependymal tumors, and multiple tumors of the heart, kidneys, skin and other organs.

Though the disease was described by several authors before 1900, von Recklinghausen reporting a case as far back as 1862, the minute histologic alterations and their significance were appreciated first in 1912 when Bundschuh[1] and Bielschowsky[2] independently gave us very complete and exact studies founded on the embryological concepts laid down by Ranke.[3] But little has appeared in English or American literature on the subject, although Campbell[4] described it in his work on cerebral sclerosis, and Sailer[5] collected twenty-eight cases in 1898. One American writer recently described a case as juvenile multiple sclerosis. It is important that these cases be recognized, for in addition to the epileptic seizures, these patients often present focal symptoms that may call for operation. It is the consensus of opinion, however, that operation has no favorable influence on their subsequent course.[6]

Because of the association of tumors of other organs with the focal sclerosis of the cortex, cases of tuberous sclerosis are recorded under many titles, and a comprehensive review of the literature is therefore difficult. Titular reference is in some instances to the cardiac tumors, as in von Recklinghausen's case; in others to the renal tumors; while

1. Bundschuh: Ein weiterer Fall von tuberöser Sklerose, Ziegler's Beitr. f. path. Anat. u. allgem. Path. **54**:278, 1912.

2. Bielschowsky and Gallus: Klinische und anatomische Studien über tuberösen Hirnsklerose, J. f. Psychol. u. Neurol. **20**: Suppl. Erganzungsheft 1, 1913.

3. Ranke: Beitrag zur Kenntnis der normalen und pathologischen Hirnrindenbildung, Ziegler's Beitr. f. path. Anat. u. allgem. Path. **47**:51-126, 1909-1910.

4. Campbell, A. W.: Cerebral Sclerosis, Brain **28**:367-437, 1905.

5. Sailer, J.: Hypertrophic Nodular Gliosis, J. Nerv. & Ment. Dis. **25**: 402, 1898.

6. Volland: Untersuchungsresultate von 50 Schädeltrepanationen bei Epilepsie, Ztschr. f. d. ges, Neurol. u. Psychiat. **74**:505, 1922.

still others, in which the cutaneous tumors were prominent, are found under the name of adenoma sebaceum. On an estimate, about 100 cases have been reported.

Degeneracy in the parents is an etiologic factor. The disease is congenital, but neither familial nor hereditary. Apparently it begins between the fourth and seventh fetal month. Ranke and Bundschuh have pointed out that the primary and secondary fissures which are completed about the fourth month are not distorted by the sclerotic patches, while the tertiary convolutions which develop later are involved. Bundschuh further called attention to the persistence of an external granule layer over the sclerotic areas which disappears in normal development about the seventh fetal month, and which is never present at birth.

The disease is characterized clinically by idiocy and epilepsy. Convulsions usually are the first manifest symptom. In Hartdegen's case the attacks began a few hours after birth and continued until the end, two days later. Brückner's patient, on the other hand, was 9 years old when the first convulsion occurred. When once initiated the convulsions usually continue, although they may decrease in frequency or even cease. The first attacks are usually mild, without loss of consciousness, and they may affect only isolated groups of muscles. During a period of years, however, they become gradually more severe and may even be the direct cause of death. The attacks are quite evenly spaced, are not so frequent as genuine epileptic attacks, nor so paroxysmal as those of the atrophic scleroses. At times equivalents of attacks are noted, fainting spells, maniacal attacks and so-called psychic epilepsy.

In cases in which the chief clinical expression is idiocy, development may be comparatively normal for several years. Usually the children are slow to walk or talk, but sometimes they are active and intelligent and may even attend school for a number of years. More characteristic than the cessation of development, however, is the retrograde process which follows it. The child ceases to take interest in playthings, prefers to sit still, loses the power of attention, becomes indifferent to everything which had previously attracted it, becomes untidy and often masturbates excessively.

Focal signs, such as localized pareses and contractures, muscular spasms and speech defects, are frequently present. Bielschowsky has reported a case in which movements on one side of the body were much retarded, with rigidity and tremor limited to that side. He records an area of sclerosis in the opposite basal ganglion.

Although status epilepticus is sometimes the direct cause of death, the patients usually die of intercurrent infection, especially of tuberculosis, or of gastro-intestinal disturbances. Occasionally the renal tumors, becoming excessively large, cause death. Patients with cardiac tumors usually die young.

DIAGNOSIS

Often the diagnosis cannot be made during life. When epilepsy and idiocy appear in a child, especially when they are progressive and when localizing signs appear, tuberous sclerosis should be considered. These signs are uncertain, however, and only when tumors of the skin are present is the diagnosis justifiable. In the Pringle [7] type these tumors grow on the face, are small, firm papillary growths, pale to dark red, vary in size up to 1 cm., and have a "butterfly" distribution over the nose and cheeks. The Barlow type is characterized by larger nodes, sometimes 2 cm. in diameter, usually found on the trunk. They are adenomas of the sebaceous glands. Sometimes there are abnormalities in the growth of the hair. The cutaneous lesions often appear first at adolescence, giving no assistance in diagnosis during the early years of life.

Rarer malformations occasionally found are tumors of the duodenum, spleen and liver; imperfections of the heart, such as patent ductus arteriosus, cardia trilocularis, origin of the aorta from both ventricles; ectopia testis, etc.

REPORT OF A CASE

History.—M. D., Philadelphia General Hospital, service of Dr. Weisenburg, aged 6 years. The father was 29 years of age, the mother 24 at the time of conception. Both were mentally healthy and of good inheritance, but the father was tuberculous and died two months before the child was born. Birth was natural and at full term; the patient was a well developed female child. She was breast fed until 9 months of age. At seven or eight weeks of age she began to have tonic convulsions lasting about two minutes followed by stupor of several minutes' duration. The convulsions increased in frequency for six months, then decreased and ceased at the age of 5 years. During the eleven months she was in the hospital no convulsions were recorded.

Although well formed, the child was backward, could not sit up until she was 2 years old, never learned to walk, talk or feed herself; she did not play with toys until she was 4. Her chief occupation was tearing up her clothing and putting the pieces in her mouth. She masturbated constantly. She could see and hear, but apparently recognized nobody, not even her mother. She would stop tearing her clothes when spoken to, but almost immediately resume it. She was large for her age. The head was slightly enlarged; the skin was without blemish; muscular power and coordination were good. Patellar reflexes were exaggerated. Urine, blood count and spinal fluid were normal. The Wassermann test on the blood and spinal fluid was negative.

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7. Pringle: A Case of Congenital Adenoma Sebaceum, Brit. J. Dermat. **1**:64, 1891.

Before being brought to the hospital, and during her stay there she had occasional attacks of vomiting immediately after taking food, although her appetite was excellent. She became emaciated, and finally died of inanition Jan 21, 1921. She was then 6 years old.

Clinical Diagnosis: Imbecility, hydrocephalus, enteritis.

Necropsy Record (Dr. Morton McCutcheon).—The body was that of a white girl 6 years of age, weighing 40 pounds (18.14 kg.). Bony development was normal; there was marked emaciation; rigor and livor were present. The skull was slightly enlarged and normal in shape; the pupils were equal and regular, the sclerae clear. The thorax was symmetrical, the abdomen retracted. Extremities, external genitalia and hair distribution were normal.

The thoracic organs were normal. The spleen weighed 40 gm., and was normal, as were the stomach and intestines. The liver weighed 540 gm. and was of normal size and consistence. The lower border was rounded. The cut surface showed a number of yellowish white lobules, the other lobules being brown. The discolored areas did not bulge. The pancreas was normal.

The left kidney weighed 60 gm., and was of normal size and consistence. The capsule stripped readily leaving a smooth pinkish gray surface. Striations were normal. Several pale yellow nodules were present in the cortical substance, the largest being 4 mm. in diameter. Some of them bulged distinctly on section although they could not be lifted out, and one bulged through the capsule. The consistence of these structures was that of normal renal substance. The right kidney weighed 50 gm. and resembled its fellow. The suprarenals, aorta, ureters, bladder and internal genitalia were normal.

The brain was distinctly enlarged; it weighed 1,120 gm. The calvarium and dura were normal. The pia was slightly opaque in places but not markedly thickened; it was nowhere adherent to the cortex. The frontal poles of the brain were smaller than usual and unnaturally white. They felt as hard as the normal brain after fixation in liquor formaldehydi. In the temporal, parietal and occipital lobes there were similar hard areas in which the convolutions were larger than normal, projected above the general contour, were flattened or even umbilicate on the surface and unnaturally pale. These areas were fairly sharply circumscribed, irregular in outline and bounded almost everywhere by tertiary fissures. The overlying pia was lightly attached. Except for a small area in the right paracentral lobule, the central convolutions had escaped. Hippocampus, cerebellum, brain stem and cervical cord were normal.

After fixation in 10 per cent. liquor formaldehydi, the usual section was made through the basal ganglions (Fig. 1). The hypertrophic convolutions were broader at the surface than at the base and compressed the normal gyri which lay between them (Fig. 2). The cortex of the sclerotic area varied considerably in thickness; it was distinguished from the underlying white matter, not so much by color as by difference in texture, the cortex being densely hard and the white matter porous. In the fissures the tissue was softer than on the convexity. In the white matter beneath some of the sclerotic gyri were minute areas resembling the overlying cortex. Microscopic examination proved these to be heterotopias of gray matter.

In the right frontal pole, where the area of sclerosis was most extensive, there was a multilocular cyst measuring about 1 cm. in diameter, without softening, pigmentation or obvious degeneration in the neighborhood.

The posterior horn of the left lateral ventricle measured 32 mm. across. Its external surface underlay a large sclerotic area in the temporal lobe. The cerebral tissue was here reduced to 11 mm. At the point chosen for study the
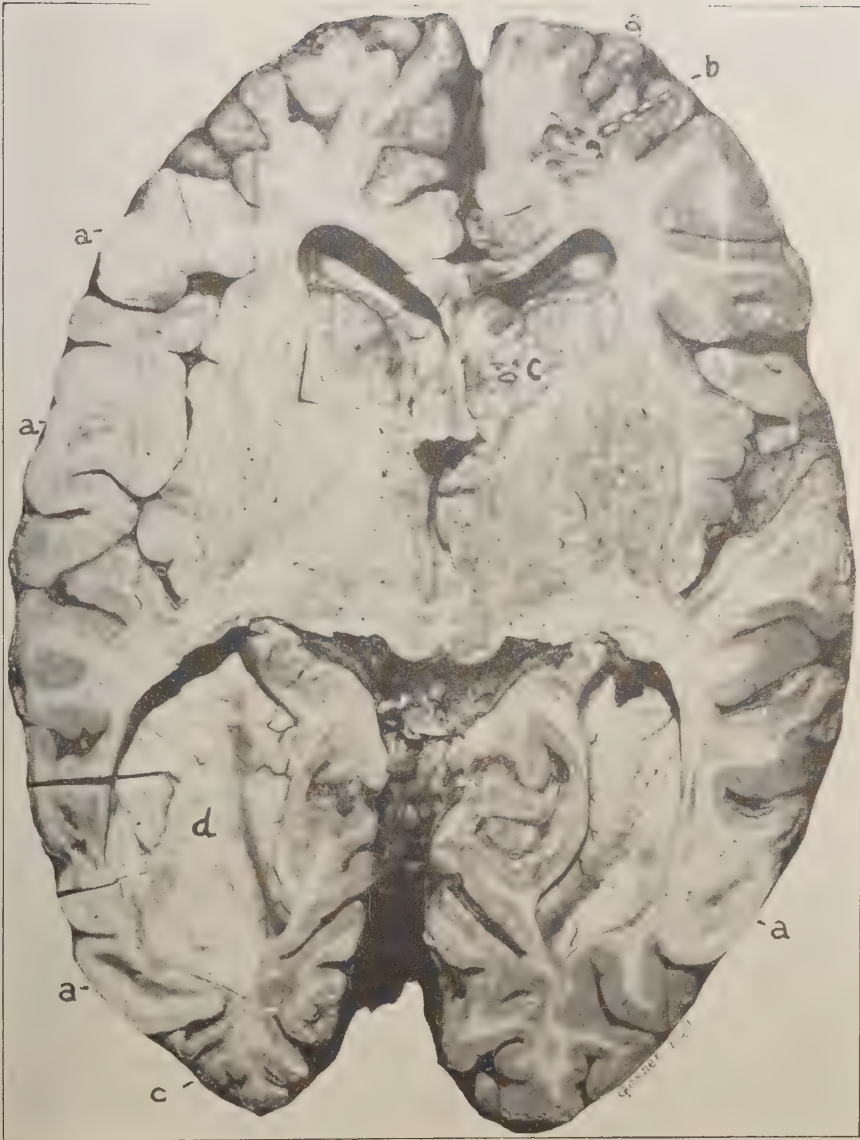
Fig. 1.—Horizontal section of brain: *a*, sclerotic areas of pale color and dense consistency with depression of underlying white matter; *b*, multilocular cyst in right frontal pole formed by dilatation of perivascular lymphatic spaces; *c*, tumor at head of caudate nucleus pressing into foramen of Munro; *d*, dilated posterior horn of lateral ventricle; note the area of microgyria in left occipital lobe.

cortex was narrow, white and hard, and the white matter was soft and porous except where the fibers of the optic radiation ran, skirting the horn of the ventricle. This tract was narrow, but apparently in good condition.

In the right parietal lobe over an area 3 by 4 cm. there were numerous abnormally small and branched convolutions, in which scarcely any white matter could be seen underlying the narrow cortex. The area was not depressed below the general level as is usual in microgyria. While these convolutions were of normal consistence and relatively normal architecture, there was a sharply defined area of sclerosis immediately adjacent. A similar area appeared in the left occipital pole.
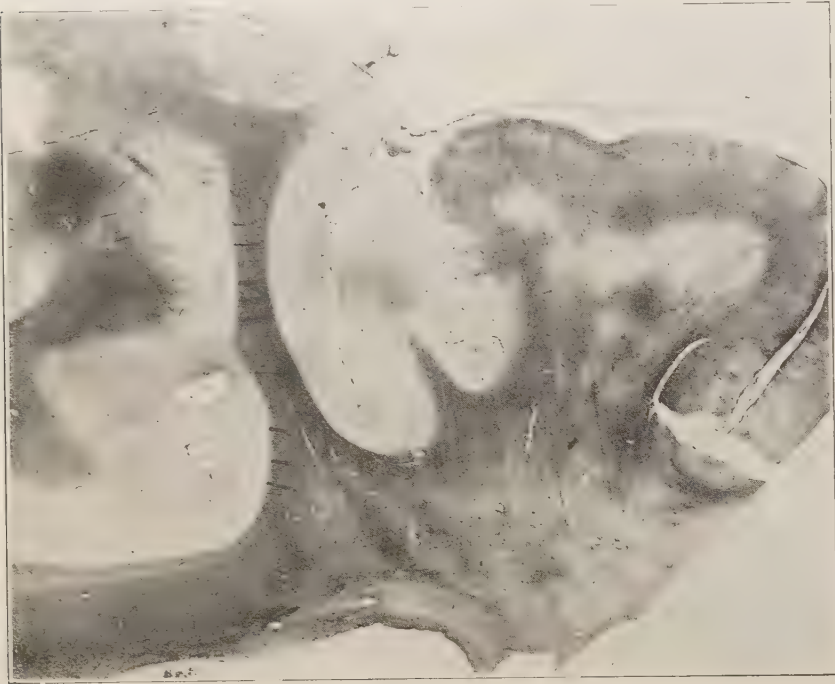
Fig. 2.—Hypertrophic convolution, broadened and umbilicate at surface, due to neuroglial overgrowth. The gliosis diminishes at the bottom of the fissure. Phosphotungstic acid-hematin stain; a, patch of beginning sclerosis.

At the head of the caudate nucleus on the right there was a tumor measuring 18 by 10 mm. pressing down into the foramen of Monro (Fig. 1). The tumor sprang superficially from the caudate nucleus, was of soft consistence, rather friable and darker than the surrounding tissue. It was circumscribed though not encapsulated. Its surface in the ventricle was fungoid and irregular, but at the sides it was smoother and apparently covered by ependyma. It did not invade the nervous tissue. At other points on the surface of the caudate nucleus on both sides there were smaller tumors varying from 2 to 6 mm. in diameter. In the third ventricle there were tumors up to 5 mm. in diameter, especially along the striae terminales. These smaller tumors occurred singly and in groups, and between the larger ones the ependyma was raised into cords.

Where a single tumor rose the ependyma was arranged in radial cords, resembling buttresses. The smaller tumors were much harder than the surrounding tissue and grated on the knife on sectioning. Between the tumor and the normal basal ganglion there was a layer of pale, firm tissue encapsulating the growth. In the vicinity of the tumors granular ependymitis was visible (Fig. 3). The fourth ventricle contained no tumors.

Gross Findings.—The gross findings corresponded closely to the descriptions given by Pelizzi, Vogt and Bielschowsky. They describe two varieties of tubera: the hypertrophic convolution and the sharply circumscribed node which has no definite cortical characteristics. These exist in varying proportions in different cases, but usually both are present. I could find none of the circumscribed nodes. Broadening of the convexity of the convolution and dimpling in the center were described by older authors, but Pelizzi was the first to show that the sclerotic process was confined to the external surface of the convolution and seldom or never reached the bottom of the fissure, even where two densely sclerotic gyri lay adjacent.
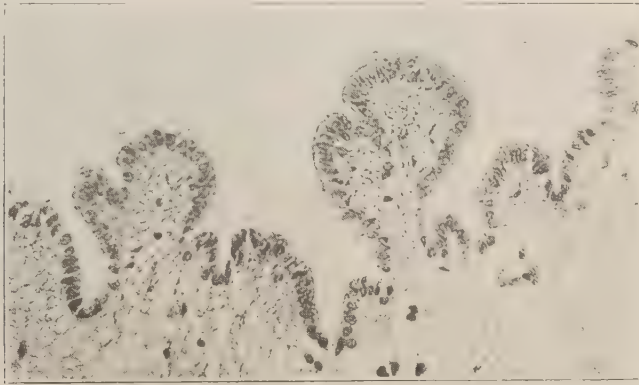
Fig. 3.—Granular ependymitis in vicinity of subependymal tumors.

The cyst of the frontal pole was unusual. Bundschuh found symmetrical cysts in the occipital poles in his case, and others have described them. Localized microgyria was described by Bielschowsky. Ventricular tumors were encountered as frequently as the cortical scleroses and did not vary much from type. They were usually hard, nearly spherical, lay immediately beneath the ependyma and varied in size up to 8 mm. Their usual locations were the caudate nucleus, striae terminales and thalamus, occasionally the fourth ventricle. On account of the persistent and uncontrollable vomiting without evident local cause, the fourth ventricle was examined with particular care but no abnormalities were found. The tumor at the head of the caudate nucleus was exceptional in size and general characteristics. Whether the hydrocephalus was the result of obstruction of the foramen of Munro by this tumor is not certain. Hydrocephalus is present in a minority of cases, and without known cause. The third and fourth ventricles were not dilated.

MICROSCOPIC EXAMINATION

Ranke [3] as a working hypothesis to explain the pathology of tuberous sclerosis suggests that there are two stages of differentiation of cells

of the central nervous system from germinal cells to fully developed ganglion cells and neuroglia cells. First, the cells develop to the point of differentiation when they become either neuroblasts or spongioblasts, and then they ripen into nerve cells and glia cells. This he acknowledges is purely theoretical, since none of the present histologic methods differentiate future neuroblasts from future spongioblasts. If the cells are disturbed at the time of differentiation, a great variety of forms may be produced. "Three extremes are thinkable: first, that the disturbance would result in the production from indifferent elements of nerve cells alone; second, of glia cells alone; and third, that no differentiation would take place. The first two possibilities are extreme one-sided differentiation, and the last, extreme lack of differentiation." Ranke elaborates the theory further by suggesting that harmful influences acting on the neuroblasts and spongioblasts at various periods of their development might produce further anomalies, and also that various combinations might occur.

The so-called "large cells" so characteristic of tuberous sclerosis are believed to be incompletely differentiated neuroblasts. They show the following anomalies (Fig. 4):

(a) Position: Some lie next to the surface; many are distributed through the cortex; some lie in the white matter, either singly or in heterotopic groups. They are seldom arranged in laminae.

(b) Size: The cells equal or exceed large pyramidal cells in size.

(c) Form: Occasionally a cell is seen that would be termed a ganglion cell were it not for its size or location. This is rare. More often the cell is round or oval, occasionally spindle-shaped or snakelike.

(d) Processes: There may be no processes or many processes, and they vary markedly in size. The large round cells have no processes as a rule, but some of them have scores resembling a Medusa's head. The spindle cells have two, and sometimes they dwarf the cell by comparison, extending full across the high power field, dividing, and wandering through the layers of the cortex (Compare Figs. 4, 5, 6).

(e) Nucleus: Many of the round cells have no nuclei. When present the nucleus is eccentric. Often it is lobed and sometimes two, three or more nuclei may be seen in a single cell. Some nuclei are small, but usually they are large; often grotesquely distorted; always pale and vesicular. Nucleoli are usually absent, and the chromatin network is very loose.

(f) Internal Structure: The round cells have neither extranuclear granules nor neurofibrillae, but the snakelike cells have fibrillae in their processes although seldom in the cell body. Sometimes suggestions of tigroid bodies are found in these more perfectly formed elements.

Investigators do not agree that these "large cells" are of neuroblastic origin. Several authors, especially the earlier ones, class them as
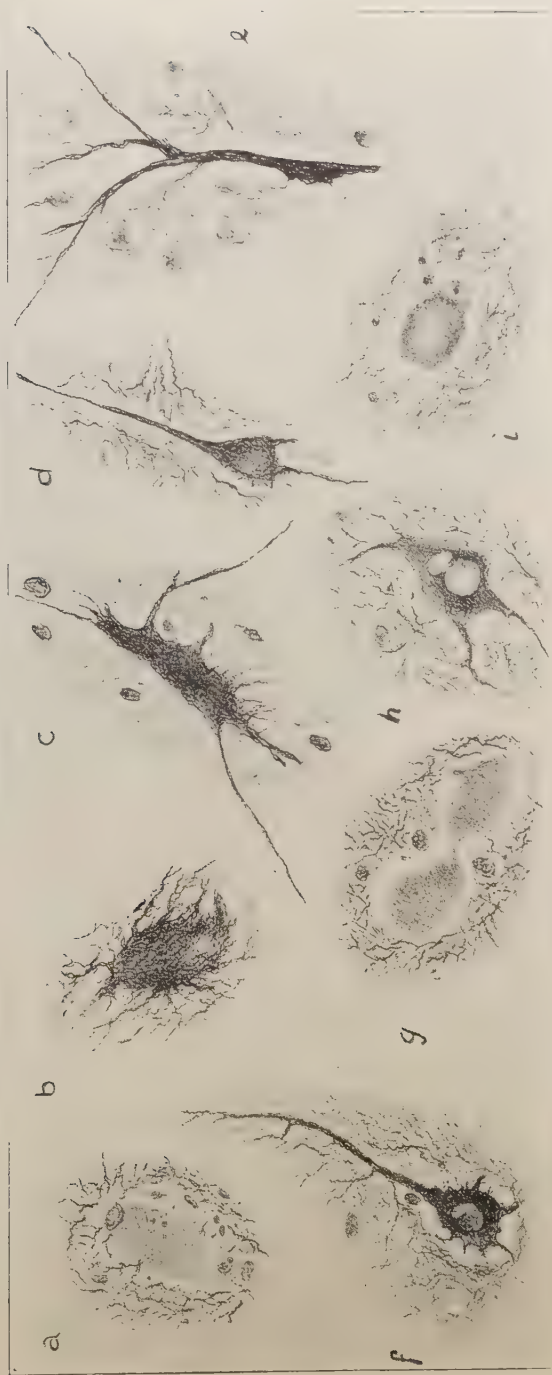
Fig. 4.—Various types of faultily differentiated cells of neuroblastic origin: *a*, simple undifferentiated "large cell"; *b*, Medusa cell; *c*, large grotesquely differentiated ganglion cell; *d*, normal ganglion cell of large pyramidal type; *e*, atypical ganglion cell; *f*, twin cell; *h*, "large cell" with bilobate nucleus from heterotopia; *i*, large cell with polar nucleus. Silver diffusion stain; × 1,000.

neuroglia cells. Bielschowsky indicates their neuroblastic origin by pointing out gradations from normal nerve cells to round undifferentiated ones on the one hand and snakelike ones on the other. Their staining reactions and the presence of neurofibrillae as demonstrated by Alzheimer also indicate this origin.
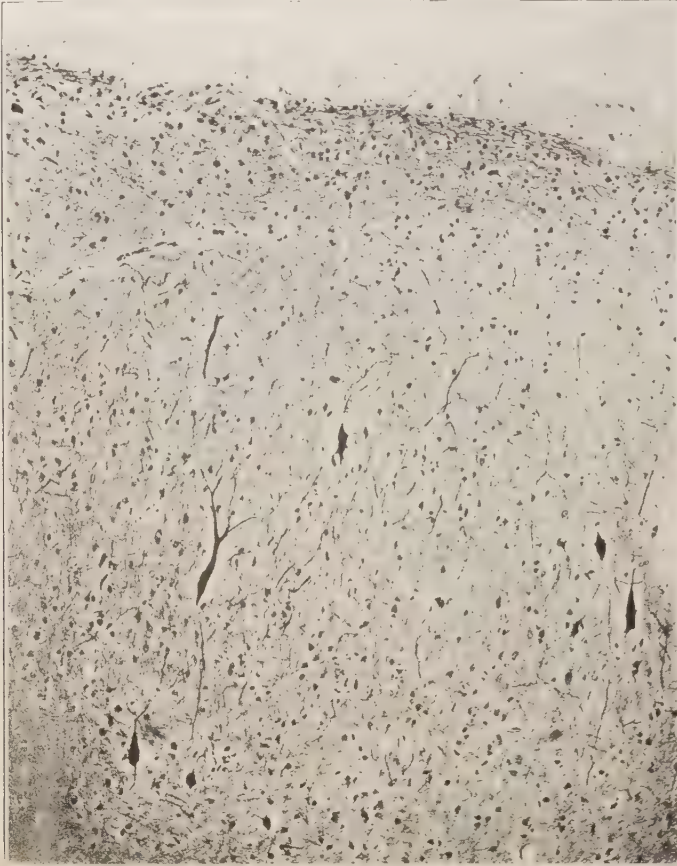
Fig. 5. — Low-power view of sclerotic cortex showing neuroglia margin, external granule layer, and atypical "large cells." Silver diffusion stain.

While these cells occurred usually in sclerotic areas, they were found also in the presumably normal cortex nearby; and they were more numerous in the deeper cortical strata and in the white matter than on the surface. The heterotopias consisted of groups of "large cells" interspersed with a few glia cells and fibers, and more or less perfectly formed nerve cells (Fig. 6).

NEUROGLIA

The density of the sclerotic cortex was due to innumerable glia fibers that intertwined in every direction. At the surface the fibers were sometimes collected into sheaves and bundles and stood on end above the normal margin (Fig. 5) but did not invade the pia. They were everywhere abundant, forming

a band many times the thickness of the normal "Randglia" (Fig. 5). At the surface of otherwise normal cortex, the first sign of sclerosis was thickening of the external glia margin and increase of glia nuclei, with sometimes a few large undifferentiated cells (Fig. 7).

Of more interest from the point of view of development was the external granule layer present in the most densely sclerotic areas. Beneath the broad surface layer of neuroglia lay a stratum of round cells, evidently glial in nature, divided from the deeper lying strata of nerve cells by another band of neuroglia fibers (Fig. 5).
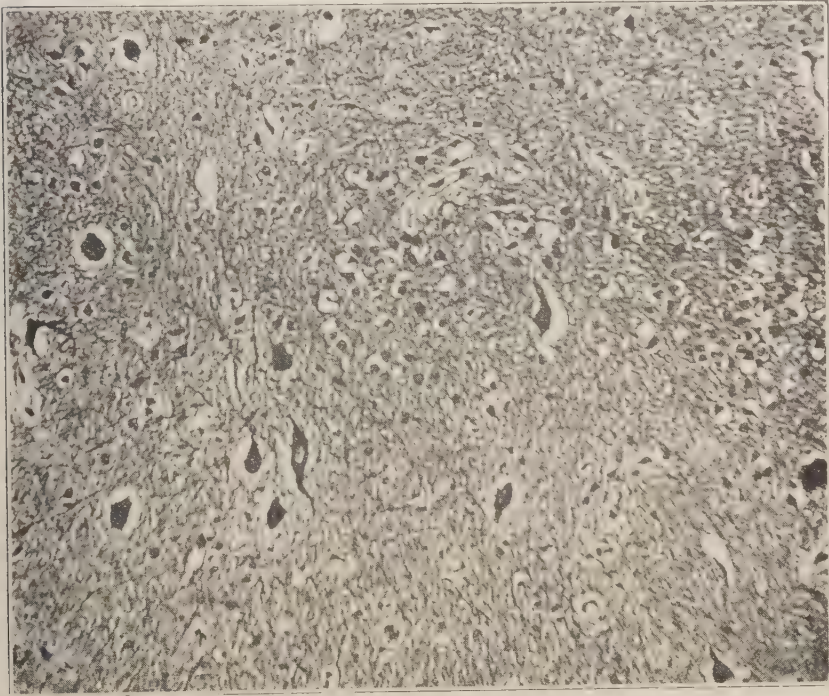
Fig. 6.—Higher power view of one of the heterotopias. Numerous atypical small nerve cells, some large grotesquely differentiated nerve cells and moderate gliosis.

Throughout the sclerotic areas there was a dense feltwork of glia fibers in the meshes of which lay numerous small nuclei. Most of these were in the resting stage but many were fiber formers. Where the feltwork was dense, it was impossible to trace the individual processes; but in the white matter where the tissue became spongy, the glia feltwork was much looser, and here the individual cells stood out with greater prominence (Fig. 8). They were larger than normal and possessed fairly definite cell bodies. The fibers were deeply stained, seemed to spring from the periphery of the cell, were heavy, and at a short distance from the cell divided dichotomously into larger and smaller branches which then curved away in easy paths and broke up into the usual glia fibers.

In the hypertrophic convolutions typical nerve cells were few, small and not arranged in strata; their apical dendrites pointed in various directions, and

Fig. 7.—Earliest sign of beginning sclerosis. Increase of marginal glia associated with a few large undifferentiated cells. Neuroglia stain.
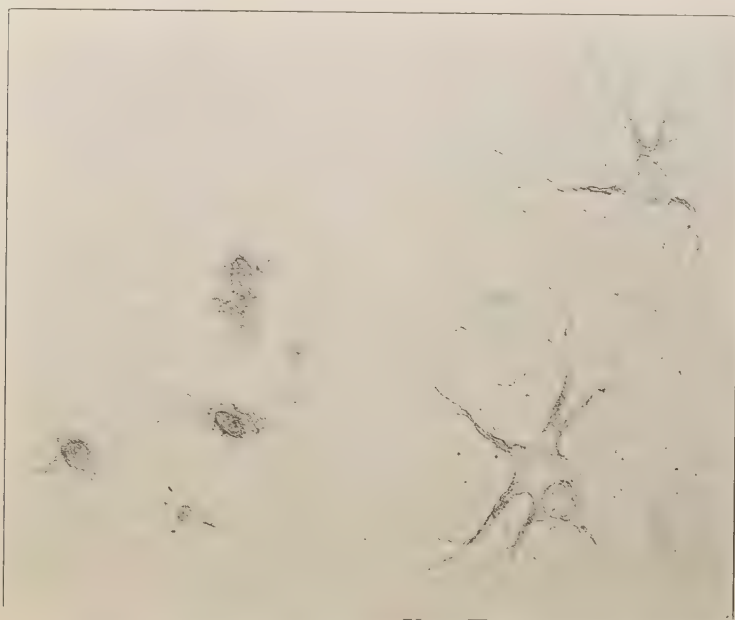
Fig. 8.—Neuroglia cells from loose-meshed white matter; very many processes extending from all points of cells; giant neuroglia cells from junction of white and gray matter; × 1,800.

they contained only remnants of internal structure. Myelin sheaths were almost entirely lacking. By silver impregnation, however, a surprisingly large number of nerve fibers was demonstrated even in the most densely sclerotic areas and the underlying loose-meshed white matter. Moreover, there seemed to be little interference with the projection tracts, for the spinal cord showed no degenerative changes, and such tracts as the optic radiation were well preserved.

Scarcity of myelin sheaths was quite as characteristic as overgrowth of neuroglia in the hypertrophic convolutions, yet in one area studied, nerve fibers appeared to be surrounded by multiple concentric rings, sometimes irregular or oval, depending on the angle of the section. These stain poorly for myelin, but clearly with phosphotungstic acid. They appear to be hyperplastic but poorly differentiated myelin sheaths.
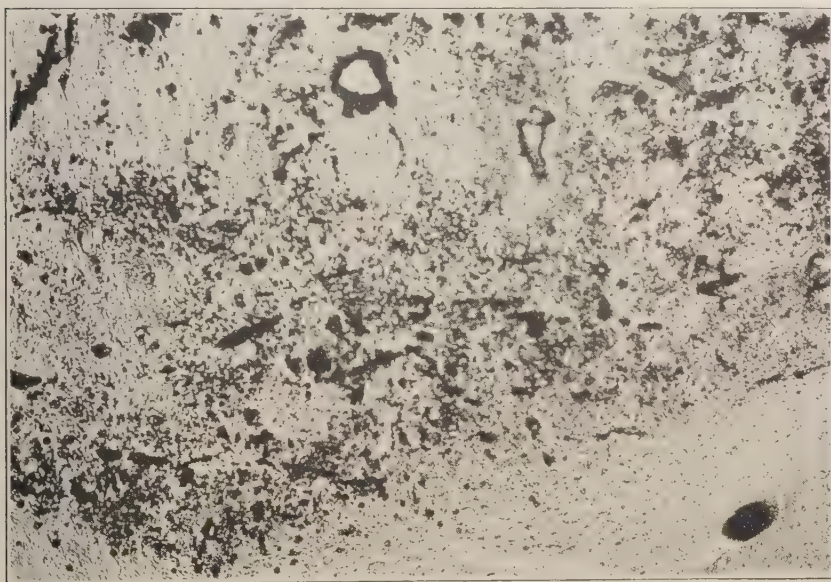
Fig. 9.—Concretions in old compact tumor. They appear to originate from blood vessels.

SUBEPENDYMAL TUMORS

All the tumors in this case except the large soft one were covered by ependyma. They arose from the subependymal glia layer and projected into the ventricle. The process of tumor formation here could be seen by examining the wall of the ventricle. The subependymal neuroglia layer became thicker, the cells developed processes, and a few large undifferentiated cells appeared, thus paralleling the picture seen in the cortical scleroses. At first the tumor was covered with ependymal cells, but as growth proceeded this layer became much flattened and rupture might have occurred so that the ependymal covering was lost. The tumors which had broken through the ependyma were more vascular and apparently of more rapid growth.

The early tumor is merely a collection of large cells with neuroglia fibers running between cells and surrounding it. In the larger tumors the cells are

more numerous and the glia fibers are proportionately diminished. They separate it into cell groups by trabeculae, and wall it off from the underlying ganglion. Many vessels in these moderate sized tumors are infiltrated with calcium salts (Fig. 9). There is granular ependymitis in the vicinity of the tumors (Fig. 3). Whether the cells of these subependymal tumors are of nervous or supporting origin is contested, some authors considering them as large cell gliomas, others as ganglioneuromas, and still others as neuroblastomas. The majority ally them with the gliomas.

The typical cells of these tumors are fusiform or retort-shaped, vary in size up to that of the largest of the Betz cells, have no tigroid bodies or neurofibrillae, and send processes away from one or both ends. Some of the
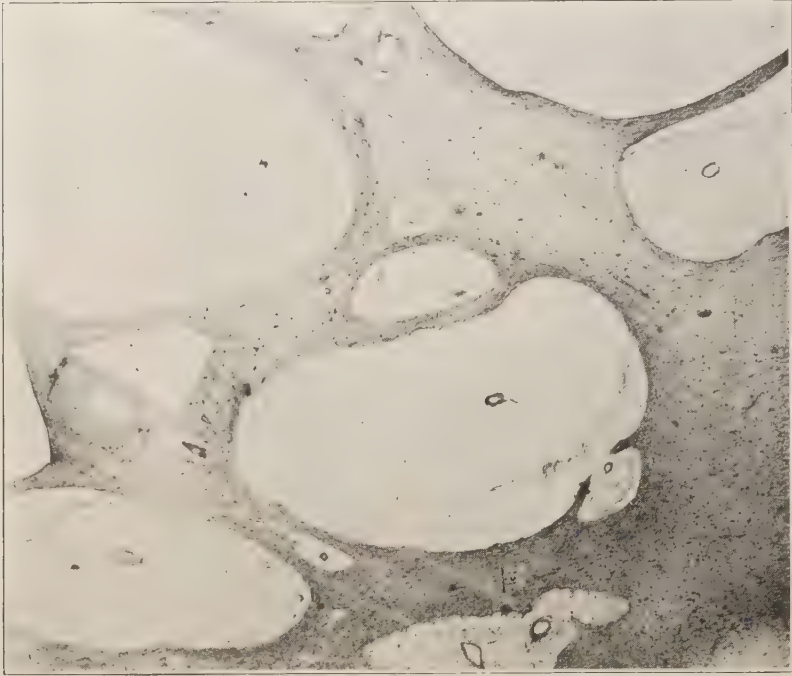
Fig. 10.—Low-power view of multilocular cyst.

cells are almost round and have no processes. The nuclei are usually large, with definite nuclear membrane, delicate chromatin network, and only occasional nucleoli. Sometimes the nuclei are grotesque in size or shape, or two or more nuclei are found in the same cell. Mitotic figures are absent. Many of the larger cells have vacuoles but otherwise do not seem to be degenerated.

The fibers sent off by the large cells run in bundles and separate the cells from one another into groups. Among these fibers lie cells of a different character, usually much elongated, with large distorted nuclei and processes following the cell outline. These take the glia stain typically whereas the large cells stain like ganglion cells.

The large tumor in this case varied in microscopic as well as gross characteristics from the others. The cells were not divided into groups, and glia

cells and fibers were almost absent. The cells were polygonal or spherical and had no processes. They stained more heavily than those of the smaller tumors, were smaller in size, and twin cells and multinucleated cells were more frequent. The extreme edge of the tumor was serrated with cell columns projecting into the ventricular lumen. There was a rich supply of vessels of large caliber and thin walls. In many respects the tumor resembled a malignant growth.

BLOOD VESSELS AND CYST

Many of the pial vessels were thickened by overgrowth of the middle coat, and the elastic lamina was split into two or more layers. There was no perivascular round cell infiltration or other sign of inflammation.

In the cortex of the sclerotic areas the blood vessels were less numerous than usual and many were abnormally thick-walled. The perivascular spaces were increased. In the white matter this increase became striking and was of two forms. In the first the adventitia was increased, filling up the space and giving the vessel the appearance of an enormously thickened wall, although the tissue was loose-meshed and nuclei were infrequent. In the other form there was further dilatation of the space to enormous proportions, without corresponding increase of adventitia, thus forming cavities (Fig. 10). This was probably the origin of the multilocular cyst of the frontal pole. Beneath a densely sclerotic cortex appeared large spaces, vacant except for an extremely delicate meshwork of fibrous tissue surrounding a small blood vessel that ran through the cavity. Between the various cavities ran trabeculae of nerve and glia fibers, with many glia nuclei in the resting stage. These septums varied in thickness down to some so fine that they were formed by only a dozen glia fibers. Moreover, in the walls of the larger spaces there were projections of glia fibers, remnants of septums which had ruptured and retracted. These cysts had no lining, and there were no degenerative changes in the adjacent tissues. They were apparently enormous dilatations of perivascular lymph spaces brought about by disappearance of nervous tissue.

CONCRETIONS

Concretions were numerous in the subependymal tumors. In the sections some of these elements were circular, intensely black spots; others had central areas of lighter color; others had lumina containing red blood cells, and still others were obviously calcified capillaries and small blood vessels. This finding has been recorded by many investigators who agree that some vessels show calcareous degeneration, but the great number and uniformity of these masses in some places has led to the suggestion that some of them are calcified nervous elements. Calcium infiltration was observed in certain large cells in the sclerotic areas. These granules were most numerous in old compact tumors with dense glia capsules and few functioning vessels. On the other hand, there was no generalized degeneration of cells, and some apparently perfect tumor cells were seen lying next the calcareous bodies. Ranke ascribes both a vascular and cellular origin to these bodies.

RENAL TUMORS

These varied in character, some consisting almost entirely of fat, others of spindle cells, others of thick-walled blood vessels. Occasionally all these

elements were found in a single tumor. They were inlaid in the renal paren-
chyma, compressed it but little, were sharply circumscribed but not encap-
sulated, and gave no hint of vegetative activity.

There were no sebaceous or cardiac tumors.

SUMMARY

The cerebral changes in tuberous sclerosis are:

1. Abnormal differentiation of germinal cells during the middle
fetal months with the production of neuroglial cerebral sclerosis and
subependymal tumors.

2. Incomplete differentiation of ganglion cells with the production
of bizarre types.

3. Persistence of the external granule layer of the cerebral cortex.

4. Agenesis of myelin sheaths in the sclerotic areas and underlying
white matter.

5. Calcareous degeneration of the walls of vessels in the sub-
ependymal tumors.

6. Localized microgyria.

In addition, in this particular case there was dilatation of the
perivascular lymph spaces with cavity formation. There was no involve-
ment of the projection tracts.

ACQUIRED DOUBLE ATHETOSIS

(Dystonia Lenticularis)

WILLIAM G. SPILLER, M.D.

Professor of Neurology, Department of Medicine, University of
Pennsylvania

PHILADELPHIA

ACQUIRED DOUBLE ATHETOSIS [*]

(DYSTONIA LENTICULARIS)

WILLIAM G. SPILLER, M.D.

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PHILADELPHIA

In 1916 I [1] reported several cases of a disorder occurring in one family, which seemed to me to belong to the group known as pseudo-sclerosis, probably a family form of a lesion of the lenticular nucleus, and in that paper I grouped the various disorders attributed to disease of the lenticular nucleus. These were the pseudosclerosis of Westphal and Strümpell, Huntington's chorea, Parkinson's disease, spastic pseudobulbar palsy with contractures and choreo-athetoid movements of Oppenheim and Vogt, and Freund and Vogt, Oppenheim's dystonia musculorum deformans, and double athetosis. To this list I added von Bechterew's hemitonia apoplectica and certain forms of carbon monoxid poisoning, and I am inclined to add a certain form of paramyoclonus multiplex resulting from lethargic encephalitis. To the list might also be added arteriosclerotic muscular rigidity and certain forms of senile dementia, which Strümpell thinks belong to his amyostatic syndrome. He refers to a paper on the arteriosclerotic form of muscular rigidity by O. Förster, but is unwilling to attribute to arteriosclerosis of the brain arteries so great causal and primary significance as Förster has done. He thinks other etiologic factors are to be considered and that while arteriosclerosis is a frequent accompanying condition, it is not a conditio sine qua non.

Nonne says that numerous findings in lethargic encephalitis show that acute inflammation of the basal ganglions may cause the amyostatic syndrome. It seems to me that the involuntary jerkings of lethargic encephalitis probably have their origin in these structures, whether they assume a choreiform or myoclonic type. A few months ago a case of the myoclonic form of lethargic encephalitis with intense muscular contractions of the myoclonic type in various parts of the body occurred in my service and terminated fatally. I found in microscopic sections a pronounced cellular infiltration of the region of the basal ganglions, but not confined to them. It occurred diffusely in the basal part of the temporal lobe. The intense perivascular

1. Spiller, W. G.: Pseudosclerosis. J. Nerv. & Ment. Dis. **43**:23 (Jan.) 1916.

cellular infiltration of the region of the aqueduct of Sylvius, so common in the usual form of lethargic encephalitis, did not occur in this case.

REPORT OF A CASE

History.—M. A., a girl, aged 16, was admitted to the Philadelphia General Hospital, Sept. 5, 1882, and died there Dec. 24, 1919. The notes taken when she was admitted stated that her father was dead, but her mother, one brother and one sister were living and well. The patient's intelligence was said to be good. When she was about 5 years of age it was noticed that she had begun to drag her left lower limb and that her left upper limb was useless. Other parts of the body became successively affected and the paralysis assumed a spastic character, the head became drawn to the left, the body arched to the left, the knees flexed and the feet placed in the position of talipes varus. Marked incoordinate movements were observed in the hands and feet; the limbs on the left side became useless, but the right hand still had some voluntary function. She could not walk and could not sit in a chair unless tied in it. Articulation was difficult and defective.

Dr. George Wilson made some notes on Jan. 29, 1915. She had been in the Philadelphia General Hospital thirty-three years. She was irritable and had an exceedingly violent temper. She objected strenuously to being exam-
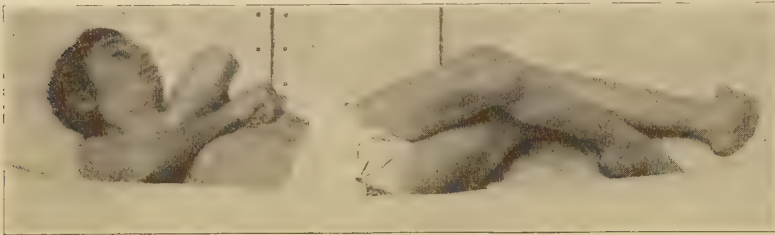
Fig. 1.—Spastic contractions with athetoid movements. These photographs were taken by Dr. Ralph Pemberton some years before the death of the patient.

ined and on one occasion called the examiner an abusive name with unusual distinctness. She had a peculiar explosive speech, which was indistinct; occasionally words were said distinctly. One who associated with her constantly was able to understand what she said. She had difficulty in chewing and swallowing and had to be fed.

Examination.—She appeared shrunken. Her irides seemed to react to light and in convergence. She had no nystagmus and no exophthalmos. Her lower jaw was frequently drawn downward and to the left and the movements were typically athetoid. Her upper limbs had little voluntary power. The fingers were tightly clasped into the palms and the forearms were supinated or pronated slowly and unevenly. The upper limbs were hypertonic and the tendon reflexes could not be obtained satisfactorily.

The lower limbs were extremely spastic and presented athetoid movements, the right foot was strongly inverted and the right great toe extended in the movements, while the left foot was placed so strongly in the position of

equinus that the toes were more posterior than the heel. Plantar stimulation gave no response except athetoid movements, which seemed more pronounced when external stimulus was applied to the feet. The patellar reflexes were not obtained on account of the spasticity. At times when the athetoid movements relaxed the entire right lower limb seemed to go into clonus. The sensation of pain was preserved.

On Feb. 21, 1916, the condition was about the same. All the limbs showed contractures and there was some muscular atrophy. Mental deterioration was marked.

On June 10, 1916, it was noted that she agreeably cooperated in the examination to the best of her ability. While mentality was poor she showed no attacks of exaltation or depression, and no errors of sense perception or of judgment.

Her muscular system was continually in a universal athetosis. The arms, hands, legs and feet were most involved and to an extreme degree, the neck was less involved, and the trunk only slightly involved. There was a spastic scoliosis. The tendon reflexes were not obtained, possibly because of the spasticity. The muscles were moderately atrophied. Both pupils showed myosis. On Dec. 28, 1916, she had periodic attacks of diarrhea. She had myocarditis and her death on Dec. 24, 1919, was attributed to this cause.
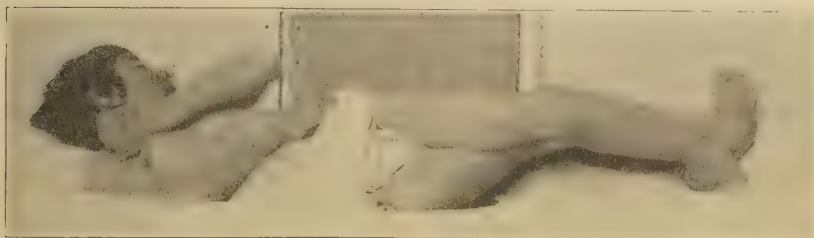
Fig. 2.—Spastic contractions with athetoid movements.

Necropsy Examination.—The necropsy examination was performed by Dr. Edward Weiss. The liver showed passive congestion; its weight was 510 gm. It was long and narrow, its surface was granular, the capsule was transparent and the substance finely mottled. It showed marked congestion of the central acini of the lobules with dilatation of the contributing sinusoids and atrophy and pigmentation of the surrounding liver cells, with slight increase in the supporting tissue. The diagnosis was chronic passive congestion and red atrophy.

The spleen showed passive congestion. It was small and firm; the interior was dark red; the trabeculae were well marked. It weighed 70 gm. It showed hyperplasia of the follicles, considerable increase in connective tissue supportive structure and splenic capsulitis. The diagnosis was chronic diffuse splenitis.

The left kidney weighed 80 gm.; the right 90 gm. They showed slight chronic interstitial nephritis. The left kidney was small and firm and cut with increased resistance; the capsule stripped with difficulty, leaving a finely

granular surface; the cortex was narrow and the cortical striations distinct. The left suprarenal gland grossly was normal. The right kidney and suprarenal gland were about the same as the left.

The length of the body was 50 inches. The brain and cord weighed 1,170 gm. They were studied by me. The convolutions of the frontal lobe were distinctly smaller than those of the rest of the cerebrum, but there were no sclerotic areas in the cortex.

Microscopic Examination.—A horizontal section was made through the upper part of the basal ganglions. Each lenticular nucleus was about one-half the normal size. The globus pallidus on each side was firm but the putamen on each side had a worm eaten appearance and contained numerous small holes. A second horizontal section was made through the cerebrum about 1 cm. below the first section, and the basal ganglions from the left cerebral hemisphere in this upper piece were cut in serial sections. The basal ganglions on the right side were cut in serial section below the second cut. As the basal ganglions from the two sides had the same macroscopic and microscopic appearance, it was not considered necessary to cut all parts of them, especially as it was desirable to keep a portion of them intact on account of their gross appearance.

Sections from the tip of the right frontal lobe were stained with thionin to determine the cellular condition. They did not show any distinct pathologic condition. The Betz cells of the paracentral lobules were greatly altered, the nucleus was eccentric and the chromatolysis was pronounced, but the smaller nerve cells of the paracentral cortex did not appear to be greatly altered. Weigert hematoxylin sections of the paracentral lobules were normal.

The nerve cells of the left island of Reil were in good condition. Nowhere could an increase in size of the neuroglia nuclei be found. The left putamen was made up of shreds of tissue containing numerous neuroglia nuclei but only here and there a nerve cell, small and much altered, was found. The Weigert hematoxylin stain showed numerous separate, wavy, medullated fibers in the putamen, each fiber standing out distinctly on the brown background. The blood vessels of the putamen were much thickened and the perivascular spaces were much enlarged.

The globus pallidus was atrophic, as was also the nucleus caudatus, but neither showed the peculiar tissue seen in the putamen. The external and extreme capsules were well defined by the Weigert hematoxylin stain. The internal capsule, both the anterior and posterior limbs, was normal. The thalamus was about normal in size and appearance.

The putamen of the right side of the brain showed the same condition as that of the left side. The perivascular spaces within it were greatly enlarged. The globus pallidus, aside from a diminution in the number of medullated nerve fibers and a smaller size, was not greatly altered. The ansa lenticularis was probably a little smaller than normal. The cells of the nucleus ruber were in good condition and the nucleus was of normal size. The corpus dentatum appeared to be normal, but the cells were much pigmented. The anterior cerebellar peduncles were normal.

The nerve cells in the anterior horns of the spinal cord in the cervical and lumbar regions by the thionin stain appeared on the whole to be normal, except that here and there an intensely altered cell was found, in which the cell body was swollen, the nucleus was displaced and chromatolysis was pronounced. The pyramidal tract was normal throughout the brain and spinal cord.

DIFFERENTIAL DIAGNOSIS

Lenticular Degeneration.—When one reads the clinical description Wilson [2] gives of his progressive lenticular degeneration, the resemblance to bilateral acquired athetosis is striking. He says: It consists of involuntary movements, nearly always a bilateral tremor of both upper and lower extremities, the head and trunk also being sometimes involved—a tremor usually rhythmical but occasionally irregular, and increasing with volitional movement; there is pronounced spasticity of the limbs and of the face, the latter being usually set in a spastic smile, while in the later stages contracture of the

Fig. 3.—Normal section through the basal ganglions. Compare this with the section represented in Figure 4 taken at about the same level from the case of double athetosis.

limbs develops; there is dysphagia and dysarthria, the latter eventually degenerating into complete anarthria; there is sometimes spasmodic laughing and emotionalism. As a result of the extraordinary degree of stiffness of the musculature there is considerable difficulty in maintaining equilibrium. Little or no true paresis or paralysis occurs, however, as most ordinary movements, if not all, can be executed, though it may be slowly and feebly, and there is some weakness. In some cases certain mental symptoms, of a transitory nature, manifest themselves. There is no sensory disturbance and no alteration in the cutaneous reflexes. If the abdominal reflexes are absent (apart from muscular rigidity) or the plantary reflex is of

2. Wilson: Brain **34**:295, 1912.

the extensor type, the syndrome is no longer pure. This, Wilson holds, is the clinical picture in pure, uncomplicated, bilateral lesions of the lenticular nucleus, and more generally of the corpus striatum, provided they are of sufficient size and of adequate duration.

Wilson says Gowers, Ormerod, Homen and he (Wilson) have been struck by the odd way in which the patients, seemingly so inarticulate, have occasionally been able to utter words or phrases with comparative ease and distinctness. This was especially observed in my case of double athetosis when, on one occasion, the patient said "damned fool" with great distinctness, whereas usually she could hardly be understood.

The lesions Wilson found in the lenticular nucleus in his cases consist of glial overgrowth which disintegrates and breaks down; there is often an immense increase in glial nuclei; the nerve fibers and nerve cells of the normal nucleus disappear; "Körnchenzellen" and macrophages are frequently present in numbers. Even when the cavity formation is extreme there are no signs of obliterative endarteritis in the blood vessels, the perforating lenticulostriate vessels and their branches. In advanced cases there are degeneration of the ansa lenticularis, relative atrophy of the corpus Luysii, partial degeneration of the lenticular bundle of Forel and of the strio-Luysian fibers and degeneration of striothalamic fibers. Apart from the degeneration in the lenticular nucleus, the changes in the brain are insignificant. Thus, the pathologic finding is bilateral symmetrical degeneration of the putamen and globus pallidus, especially of the former. The caudate nucleus is often somewhat atrophic, but never to the same extent. The Betz cells are intact and the cerebral cortex offers little definite alteration.

Although Wilson found no important cortical changes in his cases, others have reported such findings. It is impossible to explain all the symptoms of progressive lenticular degeneration by lesions of the lenticular nucleus, and this has impressed Strümpell, who states that the psychic symptoms (dementia, excitement and other symptoms) cannot be attributed to the disease of the lenticular nucleus.

In the case of progressive lenticular degeneration reported by Lhermitte [3] the findings in the lenticular nucleus closely resembled those in my case of athetosis. He found atrophy of the putamen and caudate nucleus, and the putamen contained lacunes of disintegration. The vessels were normal in these lesions. The picture he gives of the lesions resembles the findings of my case but the putamen appears less intensely affected. He says the nerve cells of all regions of the cerebral cortex were atrophied and full of lipochrome granules.

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3. Lhermitte: Semaine méd. **32**:121 (March 13) 1912.

Schütte [4] reported a case which he thought resembled progressive lenticular degeneration, and he found decided alteration of the brain, especially of the frontal lobe, where the nerve elements were destroyed in places. The remaining cerebral cortex was diffusely affected but much less intensely. The basal ganglions showed some change in the ganglion cells and increase of neuroglia, but only in slight degree, and yet the symptoms were not essentially different from those of Wilson's cases. Schütte questions whether the lenticular nucleus is the seat of the disease. He also found the liver diseased.

In the case of progressive lenticular degeneration reported by Pfeiffer,[5] in addition to lenticular lesions the cerebral cortex was much altered. The ganglion cells in the frontal region were more
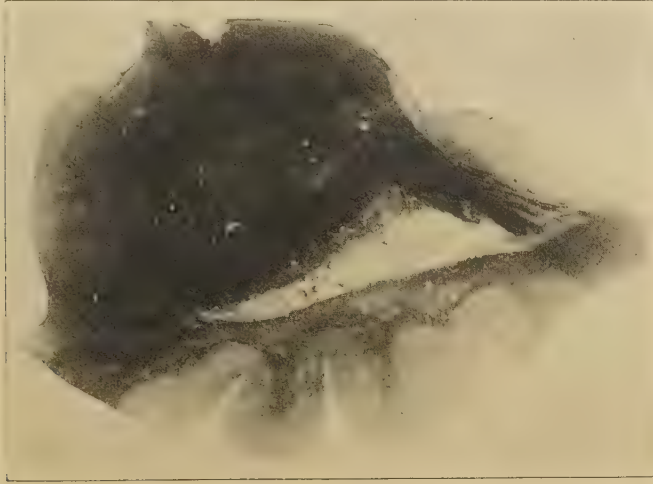
Fig. 4.—Basal ganglions from the case of double athetosis. Compare the lenticular nucleus with the lenticular nucleus in Figure 3. The section is from the left cerebral hemisphere.

severely affected than in other parts of the cortex. A swelling of the cells was observed, but shrinkage and other types of cellular disease were likewise frequently encountered, limited to the small and medium sized cells. In the motor region the giant cells were not perceptibly affected, but the commissural and associated neurons were altered.

In Pollock's [6] case of progressive lenticular degeneration, in addition to lesions of the lenticular nuclei some cortical changes were found but the Betz cells seem to have been little altered.

4. Schütte: Arch. f. Psychiat. **51**:334, 1913.
5. Pfeiffer: J. Nerv. & Ment. Dis. **45**:289 (April) 1917.
6. Pollock: J. Nerv. & Ment. Dis. **46**:401 (Dec.) 1917.

Pseudosclerosis.—The pseudosclerosis of Westphal and Strümpell apparently is generally regarded by German writers as identical or at least closely allied with Wilson's progressive lenticular degeneration, and some go so far as to refer to both conditions collectively as the Westphal-Strümpell-Wilson syndrome (Thomalla). Wilson recognized the resemblance between the two disorders in an appendix to his paper in *Brain* and in Lewandowsky's "Handbuch," and Strümpell has expressed the opinion that they are the same disease.

Otto Maas[7] came to the conclusion that no distinction could be made clinically or pathologically between the two disorders. Thomalla[8] says that in all cases of pseudosclerosis carefully studied histologically, changes were found in the lenticular nucleus, in other ganglions of the cerebrum and often in the nucleus dentatus. He asserts that von Maas and von Dziembowski have demonstrated the identity of the two diseases. I have not been able to obtain the paper by the latter author, but Thomalla referring to it says that von Dziembowski in his first case found no changes in the lenticular nucleus and attributed all the symptoms to disease of the liver and alteration of the blood; nothing is said about the method of the histologic examination.

It is therefore worth while to study some of the recent papers on pseudosclerosis. This is a term used chiefly by German writers.

Hösslin and Alzheimer,[9] in a case of pseudosclerosis, found the convolutions in general small and the sulci widened. Nowhere was cellular infiltration found. The glia of the brain was altered everywhere and there were many large glia cells. The entire central nervous system was affected, especially the corpus striatum, thalamus, regio subthalamica, pons and nucleus dentatus. The cells after alcohol hardening were stained with toluidin blue.

A. Westphal[10] in his case of this disease found alteration of the glia nuclei, especially in the basal ganglions and the nucleus dentatus of the cerebellum, corresponding with those described by Alzheimer, but less pronounced and indicating an earlier stage of the disease.

Otto Mass' case of the same disease showed bilateral degeneration of the lenticular nucleus and nothing pathologic in the optic thalamus and caudate nucleus. In the lenticular nucleus the nerve cells had almost entirely disappeared, but nerve fibers coming from outside the lenticular nucleus and entering it were preserved. The neuroglia of the lenticular nucleus showed proliferation and many astrocytes.

7. Maas: Neurol. Centralbl., 1918, No. 1, p. 16.
8. Thomalla: Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:311, 1918.
9. Hösslin and Alzheimer: Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:183, 1912.
10. Westphal, A.: Arch. f. Psychiat. **51**:1, 1913.

Maas says changes have been found in pseudosclerosis not only in the liver, but in the spleen and other glands. Fleischer, in reporting a case of pseudosclerosis, is said to have been the first to emphasize that liver changes belong to pseudosclerosis. Völsch later also pointed out the importance of the liver findings. Rausch and Schilder [11] say the liver changes in pseudosclerosis are identical with those in Wilson's progressive lenticular degeneration. The brain changes are more diffuse in pseudosclerosis, but Stöcker shows that this is not always true as he found changes in the entire brain in Wilson's type.

Rumpel [12] believed the liver which he studied from a case of pseudosclerosis was the result of fetal developmental disturbance, probably from congenital syphilis.

Fig. 5.—Section through the right basal ganglions from the case of double athetosis. The degeneration affects the putamen and the tissue consists of loose neuroglia. There is no large cavity in the putamen. It has been difficult to photograph these sections.

Athetosis and Lenticular Degeneration. — Are the changes of the nerve cells of the cerebral cortex independent of the alteration of the lenticular nucleus or are they secondary to it? It has been generally believed that no important connection exists between the ceberal cortex and the lenticular nucleus, and although this view has been difficult to accept, anatomic investigations have seemed to establish it. Wilson holds that the direct connection of the corpus

11. Rausch and Schilder: Deutsch. Ztschr. f. Nervenh. **52**:414, 1914.
12. Rumpel: Deutsch. Ztschr. f. Nervenh. **49**:54, 1913.

striatum with the cerebral cortex is minimal. Recently von Economo,[13] however, has thrown much light on this question. He believes he has demonstrated an anatomic connection between the lenticular nucleus and certain parts of the cerebral cortex, a striotemporal and a strio-parietal connection. This, he says, is contrary to the teaching of Déjerine, who denied connection from the cortex to the corpus stri-atum, and said that only collaterals from the pyramidal tract fibers entered the corpus striatum, as no cortical lesions caused atrophy of the corpus striatum, such as is seen in the optic thalamus. Von Economo holds that as there are association tracts between different parts of the cerebrum, and a lesion of one part does not cause atrophy of other parts connected with it by these association tracts, so there exists a connection between the corpus striatum and the cerebral cortex, and the tracts discovered by him, the striotemporal and strioparietal, are examples of such an association. It would be strange, he thinks, if the corpus striatum were isolated from the rest of the cerebrum except by its striofugal connections with the optic thalamus, corpus Luysii and nucleus ruber. Von Economo regards the tonic spasm without reflex exaggeration as a pathognomonic symptom of disease of the lenticular nucleus.

It is possible, therefore, that the alteration of the cells of the cere-bral cortex has a close connection with the alteration of the lenticular nucleus. The changes in the Betz cells in my case of athetosis, evi-dently far greater than any alteration of the cortex observed by Wilson in his cases, may have some connection with the greater severity of involuntary movement in my case, in which there was athetosis of an extreme type in comparison with the tremor of Wilson's cases; and yet Madame Vogt did not find intense change in the cortical nerve cells in her studies.

The most striking difference in the description given by Wilson of progressive lenticular degeneration and one of acquired athetosis is in relation to the duration of the disorder and the presence of tremor, as in bilaterial athetosis the involuntary movement is not regular and is unlike that described by Wilson; and yet in Gowers' case which Wilson accepts as belonging to his type, it is stated that the fingers at times were extended and slowly moved in the irregular way charac-teristic of athetosis. Wilson states that tremor and athetosis may occur together, but they are sufficiently distinct to be described apart. In another place he distinctly states that associated movements and athetoid movements do not occur in progressive lenticular degeneration.

It remains to be proved, I think, whether the involuntary move-ments in progressive lenticular degeneration are practically always of

13. Von Economo: Ztschr. f. d. ges. Neurol. u. Psychiat. **43**:173, 1918.

the tremor type and are characteristic of lesions confined to the lenticular nucleus. My case of athetosis is proof to the contrary, so is Fischer's [14] case of athetosis and Thomalla's case of torsion spasm; especially so are those studied by Madame Vogt in association with others. Von Economo has shown by a case of his own and by others that in progressive lenticular degeneration spontaneous movements may be entirely absent. Lenticular lesions may therefore cause involuntary movements of different types.

Wilson states, in comparing his cases with those of Madame Vogt,[15] that in his cases there were no associated movements or any type of
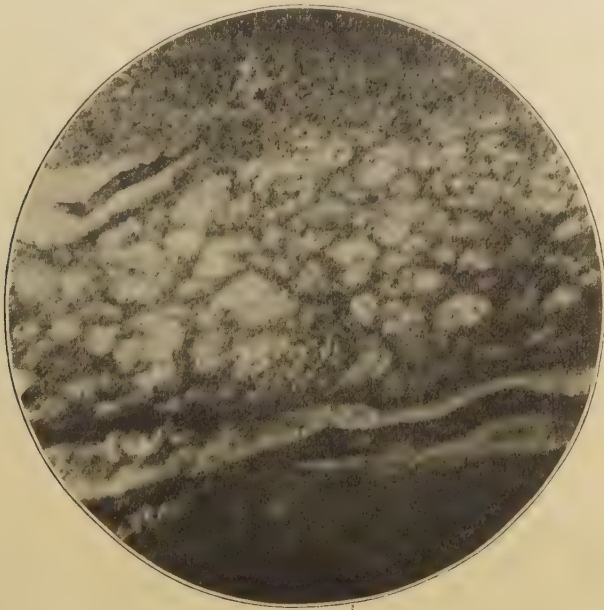
Fig. 6.—Section under greater magnification through the putamen, showing the loose neuroglia tissue. A blood vessel with an enlarged perivascular space is seen passing entirely across the section. (Photographs of the brain are by Dr. A. J. Smith.)

athetosis. These differences he regards as important, for progressive lenticular degeneration is a disease *sui generis,* and is not to be considered as a variety of "athétose double." Madame Vogt believes that the syndrome of the corpus striatum is an "athétose double pure," but Wilson is more inclined to associate tremor than athetosis with the syndrome.

14. Fischer: Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:463, 1911.
15. Oppenheim and Vogt: J. f. Psychol. u. Neurol. **18**: 1912. Freund and Vogt: Ibid.

Wilson points out that in Anton's case, which he (Wilson) asso-
ciates with cases of athetosis, the involuntary movements in the lower
limbs were more like tremor. There was therefore in this case an
association of tremor with lenticular disease.

Madame Vogt's findings are: In the case of infantile pseudo-
bulbar paralysis with athetosis reported by her with Oppenheim, the
caudate nucleus and putamen were much affected. The globus pallidus
was atrophied in its dorsal portion. The ansa lenticularis appeared
little altered. Nothing abnormal was found in the cerebellum or in
the cerebral cortex. The internal capsule appeared to be unusually
large on account of the change in the corpus striatum. Madame Vogt
thought the parts destroyed must have had a regulating and inhibiting
effect on the motor system.

In the case reported by her with Freund, the cerebral cortex showed
no noteworthy alteration. Here also was found only atrophy and
état marbré in a part of the caudate nucleus and the putamen. The
rest of the brain was intact; even the Betz cells were normal.

Cécile Vogt, depending on the case of Anton, the cases she studied
with Oppenheim and Freund and the two brains from Barré, believes
the état marbré and atrophy of the corpus striatum produce the syn-
drome of the corpus striatum, namely, double athetosis without or
almost without paralysis and without intellectual deficit or without
pronounced intellectual deficit.

Strümpell [16] reports two clinical cases in brother and sister which
he does not fully identify with Wilson's type, but brings into close
relationship with it. Rigidity was the most characteristic feature in
his cases and tremor was so slight and fine that without careful obser-
vation it would have been overlooked, and it was not always present.
In one of these cases athetosis was especially marked in the hands and
less so in the feet; in the other case athetosis was not observed in the
hands, but it was pronounced and constant in the toes though not
intense. These cases show the relation between progressive lenticular
degeneration and bilateral athetosis.

Anton's [17] case was one of chorea with athetosis. He found almost
symmetrical isolated lesions of the posterior half of the putamen of
the lenticular nucleus. The optic thalamus and internal capsule were
normal. He attributed the lesions of the putamen to thrombosis of
the several small vessels supplying the putamen and passing through
the substantia perforata. Such thrombosis might be caused in chil-
dren by cachexia and fever. He quotes Kolisko as showing that the

16. Strümpell: Deutsch. Ztschr. f. Nervenh. **54**:207, 1915-1916.
17. Anton: Jahrb. f. Psychiat. **14**:141, 1896.

arteries supplying the caudate nucleus and the globus pallidus come at a sharp angle from the anterior cerebral artery, and the current is opposite to that in this artery.

Oskar Fischer mentions that although lesions in a location typical for hemichorea are frequent, hemichorea seldom occurs. Why in one case chorea occurs and in another is wanting he cannot explain. The same kind of lesion in the same location in one case may cause hemichorea, in another hemiathetosis or hemitremor. There is no satisfactory explanation for this.

He reports a case of double athetosis of gradual development in which he found granular pigmentary degeneration of the ganglion cells in the globus pallidus of each lenticular nucleus. The boy was normal until 14 or 15 years of age, but between 15 and 17 the athetosis probably developed. The necropsy showed great diminution in the size of the globus pallidus, it appeared shrunken and was of brownish color, and was more intensely colored in its anterior portion, but showed no softening or hemorrhage. The atrophy of the lenticular nucleus was evident in Weigert sections. The cerebral hemispheres were smaller than normal, and the white matter less developed, but this was much less than the atrophy of the lenticular nucleus, although the atrophy was not equally intense in all parts of the nucleus. The putamen was distinctly atrophied but not nearly so much as the globus pallidus, which was about half the normal size. The globus pallidus was poor in medullated fibers, more so in the anterior portion, which was of much the same color as the putamen. The optic thalamus and internal capsule were distinctly smaller but the caudate nucleus showed no change.

The pallor of the globus pallidus was caused by a scarcity of medullated fibers and the small size of the medullated fibers preserved. The ganglion cells of this structure were greatly changed; in Nissl stain they were enlarged and rounded, and the nucleus was swollen and the nucleolus enlarged. The cell body contained numerous fine granules and other changes were apparent. The globus pallidus alone showed pathologic change. No changes were found in the anterior cerebellar peduncles.

LOCATION OF LESIONS IN ATHETOSIS

Schilder [18] shows that in athetosis the lesion was found in different locations, and he classifies the cases as follows:

Lenticular Lesions:

1. Anton's case in which pathologic changes were found only in the putamen of each lenticular nucleus and the left ansa lenticularis was small.

18. Schilder: Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:219, 1911.

2. Berger's case in which athetosis was confined to the right side. A cavity was found in the left lenticular nucleus.

3. Oppenheim and Vogt's case in which there was pseudobulbar palsy with athetosis and changes in the corpus striatum.

Optic Thalamus Lesions :'

1. Herz's case, in which there was athetosis on the right side. A cyst was found in the optic thalamus; the nucleus ruber, anterior cerebellar peduncle and nucleus dentatus were altered.

2. Muratow's case of athetosis. A gumma was found in the optic thalamus and the anterior cerebellar peduncle also showed a lesion.

Lesions were found in the nucleus ruber in the cases of Halban and Infeld, and Marie and Guillain.

The anterior cerebellar peduncle was affected in Bonhöffer's case.

A tubercle was found in the cerebellar hemisphere in Pineles' case.

In a case of unilateral athetosis reported by Schilder a tumor was found in the lenticular nucleus. Another lesion was found in the cerebellum.

Nonne has recently expressed the opinion there can no longer be any doubt that lesions of the optic thalamus and corpus striatum are responsible for athetosis and certain forms of chorea and paralysis agitans.

DYSTONIA MUSCULORUM PROGRESSIVA IN CORPUS STRIATUM GROUP

It is interesting to see that dystonia musculorum deformans has a pathology placing the disorder in the group of corpus striatum diseases.

In a case of this kind reported by Curt Thomalla there was intense alteration of the putamen of the lenticular nucleus. The putamen on each side was abnormally small; its tissue was below the level of the surrounding structures in a section through the brain; it was of softer consistency and was fissured (zerklüftet). The putamen showed softening, its parenchyma was completely destroyed, ganglion cells and nerve fibers had almost entirely disappeared, and the neuroglia had only partially proliferated to take its place. A spongy porous glia structure replaced the normal tissue of the putamen, in which the glia nuclei were much multiplied, and numerous fatty granular cells were in its meshes. Astrocytes were few. The vessels were conspicuous in this gliar reticulum, but were not quantitatively increased. A feeble round cell infiltration was found in the outer coat of certain vessels. The pathologic condition was sharply defined from the cortex of the island of Reil.

The nucleus caudatus showed no noteworthy change, and the bands of tissue connecting the nucleus caudatus and the putamen through

the anterior limb of the internal capsule were not altered. The globus pallidus was not appreciably altered and the cortex of the island of Reil was intact.

The liver was in a condition like that described by Wilson in his cases and in cases of pseudosclerosis. The inner structure was different and was believed to indicate a defect of development. The pathologic findings were reported only in a preliminary manner.

Thomalla's patient showed transitory but typical athetoid movements, and he refers to the fact that double athetosis has often been mentioned in association with torsion spasm. His case of torsion spasm is the first in which there has been a necropsy examination. He says the alteration of the lenticular nucleus was almost identical with that in Wilson's cases, as was also the alteration of the liver.

He quotes Oulmont as saying double athetosis is a primary bilateral hemiathetosis, almost always beginning in the first years of life, usually with idiocy. Lewandowsky believed it to be more than bilateral hemiathetosis, but on account of deficient power of dissociation it is a form of generalized but not identical associated movements. There is a rhythmical character and slowness of the athetoid movements, spasmus mobilis, strongly influenced by emotion, involvement of the face, lack of dissociated movements in the face, diplegia, disturbance of reflexes and a positive Babinski reflex. Often there are contractures. The irritative motor phenomena may persist when the patient is quiet, even in sleep. Imbecility is almost constant, but many authors have observed that the intelligence is intact.

Thomalla speaks of the clinical resemblance of his case of torsion spasm to double athetosis and says Ziehen and Schwalbe also observed the similarity between their cases and athetosis. Oppenheim also accepted a relationship between these two disorders, and spoke of transitional cases. The relationship has been recognized also by Flatau, Sterling and others.

Thomalla points out that the Babinski reflex was absent in Klempner's case of double athetosis. He regards his case as a transitional one between torsion spasm and double athetosis, as he does also Flatau's and Fischer's cases. He says the liver in A. Westphal's case of pseudosclerosis was like the liver in his own case. He calls attention to the resemblance between torsion spasm and Wilson's progressive lenticular degeneration in the muscular rigidity of the entire body, including the muscles of mastication and speech; in the predominance of the flexors with gradually developing flexor contracture, etc. The resemblance between double athetosis and Wilson's type is shown by the muscular rigidity, the gradual development of contracture, the dysarthric and dysphagic disturbances, progressive character, family occurrence and psychic disturbances.

He discusses the resemblance between bilateral athetosis, pseudo-sclerosis, progressive lenticular degeneration and torsion spasm. In all there is disturbance of tonus shown by: spasms in double athetosis and torsion spasm; muscular rigidity in Wilson's type and pseudo-sclerosis, differing in all these forms from spasms of pyramidal tract origin; involuntary movements, disturbances of speech and swallowing in all, gradually developing contracture of the limbs in all, even to complete rigidity, masklike face and boardhard abdominal muscles. In all there is disease of the lenticular nucleus. The cases of double athetosis with pyramidal tract involvement must be separated from the group. Thomalla proposes for the whole group the name of dystonia lenticularis. He says as yet similar findings in the liver of patients with double athetosis do not exist; perhaps they have been overlooked; perhaps they are really lacking. In all the groups there is absence of atrophy, paresis, electrical alteration or pyramidal tract symptoms. In many cases cerebral cortical changes have been found.

J. Ramsay Hunt [20] found as the cause of juvenile and early adult paralysis agitans progressive atrophy of the globus pallidus, consisting of atrophy and diminution in number of the motor cells of the globus pallidus, the basal ganglion of Meynert, and especially the cells of similar type scattered through the caudate nucleus and the putamen (neostriatum). The evidences of cellular atrophy were especially well marked in the large cells of the neostriatum. There was a corresponding increase of the glia nuclei and a thinning of the fibers of the ansa system—striohypothalamic radiations. The small ganglion cells of the neostriatum were intact and the pyramidal tracts showed no signs of atrophy or degeneration. Hunt found no essential lesions except of the corpus striatum in juvenile paralysis agitans.

CAUSE OF INVOLUNTARY MOVEMENTS

Strümpell explains tremor and athetosis as the result of faulty innervation of the muscles which fix a limb in any position, when the agonistic and antagonistic muscles are not simultaneously innervated to the normal degree. If the innervation of one group occurs at a different time from that of the other, involuntary movement results; tremor if the alternate innervation is regular; athetosis if it is irregular. The proper innervation of the agonistic and antagonistic muscles of a part which permits proper fixation of the part is called by Strümpell myostasia, whereas the disturbance of this innervation so that steady fixation is impossible, is called the amyostatic syndrome or myastasia. Paralysis, ataxia, spasm, which are disturbances of muscle movement, he calls in distinction, the myodynamic complex or the pyramidal tract

20. Hunt: Brain **40**:58, 1917.

syndrome. In the type described by Wilson the amyostatic syndrome is especially marked, as shown by tremor, muscular rigidity, rigidity of expression, and other symptoms.

Strümpell says that intestinal symptoms, dyspepsia, diarrhea and abdominal pain have been observed only in the pseudosclerosis or the type described by Wilson. This discussion by Strümpell is interesting, but giving all the types the name of amyostatic syndrome does not explain why they occur. This question has puzzled all students of the subject. Gowers attributed involuntary movements to lesions of the basal ganglions. Von Monakow does not believe tremor is caused by direct irritation of the pyramidal tract. He believes lesions of the corpus striatum cause irritation of the motor cortex and that from this source arise the impulses for choreiform movement. Wilson attributed involuntary movements to extrapyramidal fibers, such as are (1) in the tract from the nucleus dentatus through the superior cerebellar peduncle, to the nucleus ruber of the opposite side and from this to the outer part of the thalamus opticus and to the sensory and motor cortex. Involvement of this tract must cause athetoid and choreiform movements.

(2) In the tract arising in the nucleus lenticularis, through the ansa lenticularis in the regio subthalamica, the corpus Luysii and the nucleus ruber, from here as von Monakow's tractus rubrospinalis to the cells of the anterior horn of the spinal cord.

The movements are supposed to occur because of loss of corticopetal impulses which should pass to the cortex through the cerebello-rubro-thalamo-cortical tract. Lesion of this tract anywhere will cause posthemiplegic chorea by preventing the inhibitory impulses from reaching the cortex. This view is confirmed by the statement of deVries that extirpation of motor cortical areas in those with hemiparesis and choreo-athetoid movements causes cessation of these movements. Wilson ascribes the tremor to a destructive lesion of the lenticulo-rubro-spinal system. On account of the loss of this secondary motor tract the normal inhibiting impulse which the corpus striatum exercises over the anterior horn cells of the spinal cord are lost. The uniform innervation of the anterior horn cells is thus made impossible and stronger impulses pass to them by the pyramidal tract. Every voluntary movement increases the tremor, and this is usually true of the athetoid and choreiform movements.

SYPHILIS OF THE EIGHTH NERVE *

JAMES HENDRIE LLOYD, M.D.

PHILADELPHIA

In view of the fact that there is no affection of any cranial or spinal nerve that is more characteristic or more easily recognizable, and scarcely any other, unless it be invasion of the optic nerves, that is followed by more lamentable results, it is rather remarkable that syphilitic disease of the eighth nerve had apparently attracted but little notice among American and English neurologists until comparatively recent years. This was so in spite of the fact that Jonathan Hutchinson had called attention to it, and had even made it one of the triad of symptoms in hereditary syphilis. He had also referred to absolute deafness coming on rapidly in secondary syphilis, usually bilateral; but he had given no systematic description of the symptoms that distinguish the affection of the cochlear nerve from that of the vestibular. Gowers has an inadequate reference to the subject; he speaks of primary degeneration of the eighth nerve in locomotor ataxia, but he has little to say about acute syphilis of the acoustic nerve. The older American textbooks have only passing allusions to the subject. Mills gives a more complete, but condensed, account. He refers to the theory of Althaus that the vestibular suffers more than the cochlear nerve in tabes, due to a degenerative process, causing vertigo.

It is to the otologists that we must look for more complete work, because the subject is generally assigned to them, and there is a large bibliography. West, in Power and Murphy's "System," gives a good description of syphilis of the internal ear and auditory nerve. He seems to think that the early sudden cases are due to labyrinthitis, and the late tertiary cases to meningitis and neuritis. He gives a long bibliography. Rosenstein, in 1905, studied the changes in the auditory nerve, and found basilar gummatous meningitis. In Hazen's recent work on "Syphilis" the chapter on the ear is written by Dabney, who reviews the subject and gives many references, mostly to the otologists who have written on it. Fournier, in his work on "Syphilis," has a short chapter written by Hermet, who speaks of the rapidity and incurability of syphilis of the eighth nerve, some cases occurring as early as the fifth and sixth months after the primary infection, sometimes accompanied with paralysis of the seventh nerve. The best recent review of the subject in English, of which I have knowledge, is by Dr. G. W. Mackenzie of Philadelphia, in a paper on "Syphilis of the Inner Ear and

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* From the wards and laboratory of the Philadelphia General Hospital.

Eighth Nerve." I must leave to the otologists their own field, for I am writing as a neurologist and largely, but not entirely, from a clinical standpoint.

My attention has been called anew to this subject by the recent occurence of early and striking cases in hospital practice. This may be due in part to the intensive study of syphilis of the nervous system which has followed upon our knowledge of the spirochete and our advanced laboratory methods. We have come to know how early the spirochete may invade the central nervous system, and we are naturally on the lookout for any and all manifestations of it. Cases of deafness, tinnitus and vertigo, which formerly would probably have been promptly sent to the otologist, are now retained by the neurologist and scrutinized most closely. This is proper and necessary, because few, if any, of these cases are strictly otologic. They are primarily nervous cases; the lesion is in the nervous system; and the involvement of the eighth nerve is nearly always associated with other well marked symptoms of nervous syphilis.

CHARACTERISTICS OF SYPHILIS OF THE EIGHTH NERVE

There are certain characteristics of syphilis of the eighth nerve which the neurologist should bear in mind, particularly as he is quite as likely as the otologist or syphilologist to see these cases in their earliest stage.

First, the onset may occur early in the secondary stage, sometimes very early; and even before the secondary stage, if we are to believe Pollitzer, who claimed that he saw a case seven days after infection. Randall saw a case in which deafness occurred four weeks after an infected needle-wound of the finger. Other writers speak of its early appearance, and this has been true in my own observation, the disorder showing itself in a few months.

Second, suddenness of onset and rapidity of course are sometimes striking. The patient may become deaf in a few days. Hermet spoke of "surdité foudroyant." Dabney says that "sudden loss of hearing, generally with tinnitus, no pain, no evidence of middle-ear disease, in a young adult otherwise healthy, should be regarded as almost certainly indicative of syphilitic disease of the eighth nerve or labyrinth." This tinnitus is usually marked and most distressing, even keeping the patient awake at night. It is, of course, evidence of involvement of the cochlear nerve.

Third, the disease is usually bilateral, seldom unilateral, as Hutchinson pointed out.

Fourth, there may be a cranial polyneuritis, the seventh nerve especially being paralyzed with the eighth. Sometimes the second, third, and fifth, one or all, are involved. Nonne and others have called

attention to this fact as evidence that the affection is primarily a basilar meningitis, not a labyrinthitis as some of the older otologists taught. As evidence that we are dealing with a basilar syphilitic meningitis is the fact that severe headache, with high lymphocytosis of the spinal fluid, may precede or accompany the neuritis. But this apparently is not so in all cases.

Fifth, the two divisions of the eighth nerve may not be equally involved. The cochlear in one case, the vestibular in another, may be the more affected. This is in accord with the well-known selective action of syphilis. The vestibular nerve should always be tested by the Bárány methods.

Finally, the disease may be incurable, causing complete deafness in a short time.

THE COCHLEAR AND VESTIBULAR NERVES, THE SO-CALLED ROOTS OF THE EIGHTH NERVE

It is to be borne in mind that the eighth nerve, although usually described by anatomists as one nerve with two branches, is really two distinct nerves, each with its own ganglion of origin, its own nerve trunk, and its own separate and distinct course and distribution in the central nervous system. For a part of their course these two nerve-trunks are bound together (in the internal auditory meatus) so that they appear as one nerve, but before entering the brain-stem they separate, and form the so-called roots of the eighth nerve—but they are not roots in any true sense, because, like all sensory neurons, these have their ganglions of origin outside of the central nervous system. The cochlear nerve arises in the ganglion spirale, or ganglion of Corti, within the labyrinth; the vestibular, in the ganglion of Scarpa, which is located within the internal auditory meatus. The fact that these two so-called roots are distinct before entering the brain-stem, explains how they can be separately affected in syphilitic meningitis. The fact that the eighth nerve has no neurilemma (hence called the portio mollis) may explain its vulnerability to the spirochete, and the extreme rapidity of the destructive action.

Disease of the cochlear nerve causes deafness of various grades, which is to be determined by tests made by the otologists. It has been claimed by some that abolition of the very high and very low notes, with preservation of the intermediate notes, hence allowing the hearing of a conversational tone, is quite characteristic. This was present in one of my cases; but Mackenzie denies that it is common, and says that various notes are abolished in various cases. Appropriate tests are likely to show impairment of bone conduction. It is necessary to exclude disease of the middle ear.

The vestibular nerve presides over equilibration, and its central connections are with nuclei in the brain-stem, from which by a second relay of neurons its ultimate connections are made, especially with the cerebellum and the nuclei in the midbrain. Vertigo and nystagmus, which are normal reactions on turning and douching, are variously affected, as can usually be demonstrated by the Bárány tests. Clinically, these patients may have various forms or degrees of vertigo, but in my observation staggering gait is not common.

I do not attempt here to describe tests and reactions in detail, for this province belongs to the otologist, whose cooperation is always essential in a proper study of these cases. I believe, however, it is necessary to be on guard against hasty conclusions as to the localizing value of the Bárány tests. In my observation these tests in these cases are mainly valuable in showing alteration or complete abolition of the normal vertigo and nystagmus on turning, the inference being that the nerve trunk is implicated.

It is not to be denied that there may be a true syphilitic labyrinthitis. Some otologists seem to have held that this was the common pathology, especially in the early acute cases. It may be so also in the hereditary. cases, in which the bone also may be diseased. The distinction between disease of the labyrinth and disease of the nerve is, I understand, not an easy one, and it is a problem for the ear specialist rather than for the neurologist; but there is little doubt, for reasons which I have already given, that the meninges and nerve trunk are the seats of the disease in many cases, if not in the majority.

The following case may serve as an example of the fulminating type of this disease:

REPORT OF CASES

CASE 1.—A negro, 30 years old, had been treated in the venereal wards of the Philadelphia General Hospital in June, 1917, for a chancre and secondary eruption. At this time he had received one dose of arsphenamin. He had later a syphilitic iritis, but there is no record of any nervous symptoms at this time. He left the hospital and returned to his work, but about two months later he was taken with a severe frontal headache, which forced him to return to the hospital. The headache was the only complaint. The right pupil was rigid, the result of the iritis; the left was sluggish. The cranial nerves were normal. The knee and Achilles' reflexes were much diminished, but there was no ataxia or swaying. As a routine measure the hearing was tested; no deafness was observed. Both the blood and cerebrospinal fluid were strongly positive, and there was a very high lymphocytosis. He was given mercurial inunctions and several doses of arsphenamin. In October the report from the ear clinic stated that hearing was normal; late in November, however, the hearing was slightly impaired, but the drum membranes were normal. Under treatment the headache entirely disappeared, and the blood became negative; the spinal fluid remained positive, though the cell count was much reduced. Toward March the man eloped from the hospital and was gone several weeks, when he returned. In

that short interval he had become very deaf, to such a degree that it was difficult to speak with him. He complained much of loud tinnitus. The report from the ear clinic stated that in the right ear the involvement seemed to be confined to the labyrinth, but in the left ear the indications were that the lesion was in the course of the nerve. Bárány tests were not made, but the patient had no vertigo or staggering. Active treatment did not relieve the deafness, which indeed increased until in a short time it was practically complete. There was a smoothing out of the face and brow on the left side, due to slight paresis of the seventh nerve.

The Bárány tests may give interesting results in some of these cases, as the following instance shows. It also shows bilateral seventh nerve palsy, which in itself is a rarity.

Case 2.—The patient, a colored man, aged 23, had a primary sore in September, 1918. He was admitted in October to the venereal wards of the Philadelphia General Hospital, where he was given two doses of arsphenamin; he left the hospital against advice on December 1. Three weeks later (or about three months after the appearance of the chancre) he began to have severe and persistent headache, accompanied with vertigo and tinnitus in both ears. He was readmitted to the hospital in January, when it was observed that he had paralysis of both facial nerves, more marked on the left. Other cranial nerves were not involved (with the exception to be noted) nor was there any impairment of the spinal cord, but the Achilles' reflex on the left side was abolished. The pupillary responses were normal; there was no optic neuritis. The Wassermann tests of the blood and spinal fluid were positive, and the cell count was as high as 780. He received six doses of arsphenamin up to March, 1919. The positive but shortened Rinne's test, with loss of intermediate notes, pointed strongly to involvement of the nervous mechanism; but the patient heard ordinary conversation. Dr. Lewis Fisher reported total absence of response after douching and turning, which would indicate a lesion of the eighth nerve (vestibular division); but a definite presence of vertigo after turning, as well as a preservation of a fair amount of hearing on both sides, showed that the eighth nerves were not involved in their entirety. Dr. Fisher suggested a bilateral lesion of the brain-stem on the mesial aspect of Deiters' nucleus, thus allowing the escape of the fibers for vertigo and most of the auditory fibers; but the involvement of both seventh nerves was against this view, for it clearly indicated a peripheral lesion of the so-called roots of the eighth nerves, especially the vestibular, along with the seventh nerves, in a syphilitic meningitis. As already said, it is quite conceivable that these two roots may not be equally involved in a meningitis. It is noteworthy that this patient's seventh and eighth nerve involvement showed itself three months after the primary lesion, and after he had received two doses of the arsenical drug.

The following case is of especial importance because it is the only case in the series in which it was possible to examine the eighth nerve under the microscope. It is also of much clinical interest. As in the two preceding cases, the patient was under observation from the time of the initial lesion.

Case 3.—The patient, a white man, aged 48, was admitted to the venereal wards in September, 1918, with a primary sore. He received five doses of arsphenamin. In March, 1919 (six months after the primary sore), he began

to have a staggering gait, which caused him to fall to the left. Trouble with hearing had commenced earlier in the right ear, in which he had become quite deaf; later the left ear failed. There was loud tinnitus. The blood Wassermann reaction was reported negative, but the spinal fluid was $+ + + +$. The cell count was 910. There was complete abolition of the left Achilles' jerk, just as in the other case (an odd coincidence). A low-grade double optic neuritis was present, but the pupils acted normally. The frontalis muscle on the left was smoothed out. All the other cranial nerves were normal. Dr. Fisher found that the right labyrinth was completely, the left partly, involved. There were no reactions to turning or douching. The case seemed to be a clear one of peripheral involvement, that is, of the labyrinths and eighth nerves in both divisions. The earliest symptoms appeared in less than six months after the primary sore. This man was taken with acute appendicitis and died. Under the microscope the eighth nerves were seen to have been affected, as shown in the following report.

Neuropathologic Report (by Dr. N. W. Winkleman).—Pathologic study was made of sections from representative areas of the cerebrum, cerebellum, pons, medulla, spinal cord and the eighth nerves. The stains used in this study were: a hematoxylin-eosin, Weigert's myelin sheath stain, Mallory's phosphotungstic-acid-hematoxylin and Alzheimer-Mann.

The cerebrum and cerebellum are normal, especially in so far as syphilis is concerned. The pons is negative. In the medulla there is seen a round cell infiltration (lymphocytes) in the nucleus vestibularis lateralis (Deiters') with fatty degeneration of the nerve cells of this nucleus on the right side. The membranes are normal. The spinal cord is negative.

Both eighth nerves show some swelling and tortuosity of the axis cylinders, as seen in longitudinal section, with some dropping out of axis cylinders as seen in cross section. There are present within the nerves large, round, vesicular, pale staining nuclei with irregular, indefinite, pale, acid-staining cytoplasm—in all resembling glia cells, and in places fibers are seen coming off the cytoplasm. Besides these there is present another type of cell: a long, narrow, heavier staining nucleus with a definite outline to its rather meager cytoplasm—a so-called sheath cell. At certain places within the nerves is seen a slight but definite lymphocytic infiltration. Amyloid bodies are present to excess. Around some of the vessels within the nerves are a few plasma cells with many lymphocytes. The sheath of the nerves shows a very definite though not very heavy infiltration with lymphocytes.

Diagnosis: Syphilis of both eighth nerves with involvement of Deiters' nucleus on the right.

The following case, which occurred in the service of Dr. Charles S. Potts, showed improvement under treatment with neo-arsphenamin (five doses) and mercurial inunctions. It was a late tertiary case.

CASE 4.—A white man, aged 56, began, one month before admission to the hospital, to have deafness, with vertigo and tinnitus in both ears. He also had impaired sight in the right eye and slight paresis of the right seventh nerve. There was a history of a primary sore fourteen years before. The left pupil was sluggish and irregular, the right inactive to light. Sight was much impaired. The right optic disk was much congested, with blurred margins. The Bárány tests revealed horizontal nystagmus to the left, four seconds; to

the right, four seconds. The tests of the blood and spinal fluid were positive on two examinations, but the cell count was low. Improvement was rapid under treatment. There was return of function of the vestibular, as well as of the cochlear, nerve. When discharged, the man could hear and see fairly well. It is noteworthy that this was a tertiary case of long standing, and that there was no lymphocytosis. This probably puts it in a separate class from the acute cases, already described, coming on in the early secondary stage, with headache and high lymphocytosis, indicating a rapid and acute involvement of the meninges.

CASE 5.—Another patient in Dr. Potts' wards was a negro, aged 28, who had become deaf rapidly, and who also had paralysis of the right seventh nerve. The pupils were irregular and sluggish. The clinical notes are not very full, as it was almost impossible to communicate with the patient, and he soon began to show mental symptoms, for which he was transferred to the department for the insane. No history of a primary sore could be elicited; the laboratory reports for blood and spinal fluid were negative, but there was a high lymphocytosis. He may have had a syphilitic psychosis. The onset of rapid and complete deafness in a young adult, with tinnitus, without obvious cause, and without disease of the middle ear is, as Dabney pointed out, significant of syphilis; and I may add that this is especially true if there is also a paralysis of the seventh nerve.

CASE 6.—This patient's condition was of five years' duration. He was a white man, 31 years old. He had bilateral seventh and bilateral eighth nerve paralysis and anesthesia on the right side of his face. The blood reaction had been reported several times as strongly positive. He had come and gone to and from the hospital four or five times; consequently the course of symptoms had not been accurately traced. His condition was evidently incurable, and illustrated the lamentable fate of a patient with this syphilitic syndrome. He was almost totally deaf, with paralysis and contractures of both sides of his face.

EFFECTS OF ARSPHENAMIN ON SYPHILIS OF THE EIGHTH NERVE

In discussing this affection, the subject of neurorecidivus, or the spinal fluid changes in neurosyphilis caused by a provocative dose of arsphenamin, inevitably occurs to the mind. The first three of the foregoing series of cases suggest this possibility. Another thing to be considered is the possible injurious action of the drug itself directly on the nerves. This charge has been made against this arsenical preparation not only in the case of the eighth nerves, but also in the case of the optic nerves. When, however, it is considered what a large number of injections of arsphenamin are being given every day, and what a comparatively small number of such complications occur, the inference that the drug is the cause is hardly warranted. Mackenzie criticizes the statement, made by some observers, that this affection of the eighth nerve has been caused by arsphenamin, and combats it. He believes that such cases are instances in which the treatment has not been sufficiently active. In the discussion of a paper by Klauder on this provocative action of arsphenamin, read before the Philadelphia

Neurological Society recently, Solomon said that Crockett, of the Massachusetts Eye and Ear Infirmary, had made a study of syphilitic nerve deafness before the arsphenamin era and after, and found the incidence about the same, if anything a little less, since the use of this drug. The absence of the Achilles' reflex on one side in two of the cases is noteworthy in this connection. Beeson [1] in a recent paper refers to abolition of the Achilles' reflex as a danger signal in treatment with arsphenamin. It may indicate a peripheral neuritis due to arsenic.

Under the microscope the appearance of the tissue is distinctly that of syphilis, as shown by the lymphocyte infiltration; but there is also the appearance of alteration of the nerve-fibers which is at least suggestive of the action of a poison.

1. Beeson, B. B.: Polyneuritis Plus Dermatitis Exfoliativa Following Neo-Arsphenamin, Arch. Dermat. & Syph. **2**:337 (Sept.) 1920.

A CLINICOPATHOLOGIC STUDY OF ACUTE AND CHRONIC CHOREA *

GEORGE WILSON, M.D., AND N. W. WINKELMAN, M.D.

PHILADELPHIA

Our main object in presenting this paper is to report the pathologic findings in two cases of chorea, one of the acute and one of the chronic variety. Until recent years the pathology of these two conditions has been elusive, and even today we do not have a clear conception of the underlying anatomic changes of the choreas; this is especially true of Sydenham's chorea.

Until Marie and Tretiakoff, in 1920, reported their case of Sydenham's chorea there was practically no known pathology in this condition so far as the nervous system was concerned. These writers described in their case findings identical with those seen in patients who died of epidemic encephalitis. In fact, as one reads the report of Marie and Tretiakoff one wonders whether their case was not one of the choreiform type of encephalitis.

One of us saw a case in the winter of 1920-1921 which he diagnosed as a severe case of Sydenham's chorea in a boy of 14, who later in the course of his disease developed lethargy and other typical signs of encephalitis from which he made a complete recovery. Had this patient died in the first stage of the infection, he would have been considered as having had Sydenham's chorea, and yet the outcome proved beyond a doubt that it was a case of epidemic encephalitis. As further evidence that Marie and Tretiakoff's case was not one of acute chorea may be mentioned the fact that there were no signs of endocarditis.

The possible relation between chorea and encephalitis has been discussed by Harvier and Levaditi, whose conclusions are: "1. Certain acute febrile choreas are brought about by the virus of encephalitis. 2. It is not yet proved that *all* acute febrile choreas are due to this agency."

REPORT OF CASES

CASE 1.—*History.*—A patient with Sydenham's chorea was admitted to the medical service of the hospital of the University of Pennsylvania on July 4, 1920, and was assigned to the service of Dr. Alfred Stengel.

The patient was under the care of Drs. Stengel and Wolferth, and we are indebted to these gentlemen for the privilege of reporting this case, and for the use of the pathologic material obtained from it.

On June 19, 1920, the patient, who was a girl, 12 years of age, began to have involuntary jerkings of the upper extremities. Two or three days later

the movements involved the head and the tongue and then the lower extremities. At the time of her admission to the hospital she could not talk and was confined to bed. Physical examination revealed a well nourished child with typical choreiform movements involving all four extremities, the trunk, the head and the tongue. A systolic murmur was heard at the mitral and pulmonic areas. The blood examination showed an eosinophilia of 6 per cent.

Fig. 1 (Case 2).—Horizontal section of hemispheres, showing dilatation of ventricle and atrophy of caudate and lenticular nuclei.

For six days following her admission her temperature was at or near normal, but after that it showed some variations, the temperature going as high as 101 to 102 F., and even as high as 105 degrees before death.

Necropsy Examination.—This revealed vegetations, semisoft but well attached on the auricular side of the mitral leaflets. These vegetations averaged 1 to 2 mm. in size. All the other valves were normal. A thorough and systematic

examination was made of the brain with special reference to the basal ganglions. In this study the toluidin blue, Weigert; phosphotungstic acid hematoxylin, Alzheimer-Mann, Marchi, Bielschowsky and hematoxylin and eosin stains were used. It is entirely proper to state at this point that absolutely no changes were found in the brain that could not be attributed to the acute febrile condition from which the patient suffered for some days before death. No changes were found which in any way approached the findings which Marie and Tretiakoff described in their case of Sydenham's chorea, a case which was probably one of epidemic encephalitis.

Fig. 2 (Case 2).—Basal ganglions. Note atrophic striatum, caudate nucleus and putamen and absence of internuclear fibers. *Nc.* indicates the caudate nucleus; *Put.*, the putamen; *Thal.*, the thalamus. Weigert stain.

CASE 2.—*History.*—The case of chronic chorea which we have to report is that of a man who was a patient in the Philadelphia Hospital for some years. He died on the service of Dr. T. H. Weisenburg, and we are deeply indebted to him for the courtesy which he has extended in permitting us to use this valuable case.

A white man, 52 years of age, was admitted to the Philadelphia Hospital on Jan. 25, 1905, and died on March 3, 1917. His family history is one showing a marked degenerative defect as eight of his blood relations have had Huntington's chorea; other members of the family have been insane. The man's choreiform movements began in 1910, and shortly afterward he began to show mental symptoms, chiefly those of a simple dementia. The choreiform movements affected his entire body, and involved to a marked degree the muscles of his trunk and pelvis. His gait was rendered extremely bizarre

by these movements, the unusual thing in his gait being a series of bowing movements. Some considered this a case of dystonia musculorum deformans.

Necropsy Examination.—The brain appeared to be what we have chosen to call "paretic looking." The cerebrum, cerebellum, brain stem and spinal cord were smaller than normal. The convolutions were atrophic and the fissures widened, this being especially evident over the frontorolandic areas. The pia-arachnoid was everywhere thickened, but to a more marked degree over the anterior half of the brain where it concealed the underlying structures by its opacity. Decortication could be performed without tearing the cortex.

Fig. 3 (Case 2).—Putamen, showing typical astrocytes. *B.* Phosphotungstic acid hematoxylin stain; × 368.

Cross section of the brain in the usual manner showed that the ventricles were dilated (Fig. 1) and that the basal ganglions were small in proportion to the rest of the brain. The cortex was visibly narrowed, especially anteriorly.

The microscopic method of examination included large sections from different areas of the cerebrum, brain stem, cerebellum, spinal cord and serial sections through the basal ganglions and hypothalamic region. The stains used were the same as in the preceding case.

The Cortex.—Weigert stain showed atrophic convolutions separated by widened fissures and a narrow cortex with loss of many of the myelinated

fibers in all layers, most noticeable anteriorly. With toluidin blue the cyto architecture was profoundly altered, so much so that the normal relationship could not be recognized. An occasional Betz cell remained to identify the motor area. The ganglion cells throughout, but especially in the fronto-rolandic cortex were decreased in number, and diseased. Those which remained exhibited various forms of acute and chronic cell change, such as simple chromatolysis, axonal degeneration, Nissl's severe cell disease and atrophy. The silver impregnation stains confirmed the findings obtained with toluidin blue. The vessels were not increased in number, but they showed distinct

Fig. 4.—Normal putamen. Note satellitosis around large ganglion cells at *A*. Toluidin blue; × 57. (Use hand lens.)

sclerosis and hyaline degeneration; for the most part the perivascular spaces were dilated, containing only the products of brain degeneration which at first glance simulated the cuffing with lymphocytes and plasma cells found in paresis. Glia cells were increased in number.

The pia-arachnoid showed distinct thickening, due to a connective tissue proliferation and containing within its meshes cells which on differential stain-ing proved to be gitter cells with a tendency to agglutinate in the region of

fissures and about the vessels. Amyloid bodies were present, especially in the outer layers of the cortex and in relation to the ventricles, showing that there was a slow degenerative process going on. Although sought for, no foci of degeneration were found as described by Klebs, Oppenheim and Hoppe, Marie and Lhermitte and others; nor were plaques found such as are seen in senile dementia and at times in senility. The central white substance showed atrophy of the projection system of the cortex with replacement by neuroglia fibers arranged similarly to the destroyed fibers, showing that the process had taken place slowly.
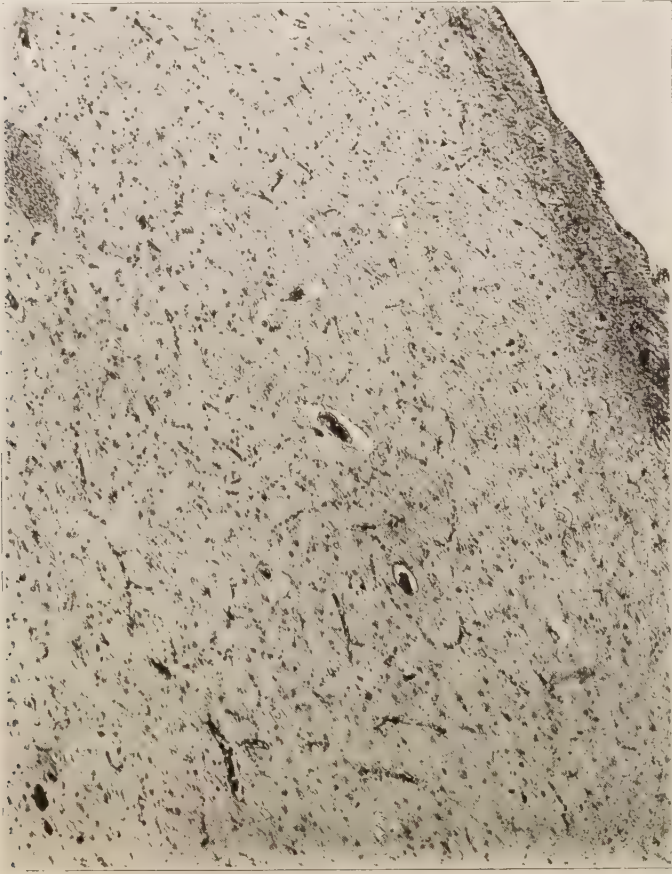
Fig. 5 (Case 2).—Caudate nucleus. Note intense glial infiltration. Phospho-tungstic acid hematoxylin stain; × 57.

The Cerebellar System.—In the study of large sections of the cerebellum, including serial sections of the dentate nucleus, nothing of note was found except a smallness of all the structures. There were no areas of softening. The pontile nuclei, red nuclei and olives were intact.

The Central Ganglions.—As shown in Figure 2, with the Weigert stain there was marked atrophy of the central ganglions, particularly of the caudate and lenticular nuclei. As can be seen, the caudate was distinctly shrunken; the

putamen was apparently more involved than the globus pallidus. The thalamus was relatively intact. The internal capsule stained well, showing no areas of degeneration, and its dimensions were in proportion to the size of the brain. The internuclear fibers which take origin in the small cells of the caudate nucleus and putamen (the striatum of C. and O. Vogt) were absent. Serial sections through the hypothalamic region revealed no degeneration of the projection fibers (striothalamic, striosubthalamic and striomesencephalic radiations).

More minute histologic study showed that the nerve cells had practically all disappeared from the caudate and putamen, with only a few of the smaller and some of the larger motor type (Malone) of cells remaining. The phospho-tungstic-acid hematoxylin stain showed an extreme proliferation of the glial elements, especially of the astrocytes (Fig. 3), which had a tendency to collect about the vessels. As could be seen in the gross, the globus pallidus (the pallidum of C. and O. Vogt) was much less involved. The characteristic large cells were present in the usual number. Glia cells were slightly increased, although astrocytes were rare. In the thalamus, there were atrophic lesions of the cells with a glial proliferation, but infinitely less intense than in the striatum. The vessels showed the same changes as found in the cortex—thickening of their walls, and occasional perivascular collections of degenerated material. No foci of degeneration were seen.

The spinal cord showed no pathologic condition, and the liver, except for congestion, was normal.

<center>COMMENT</center>

The changes found in the case of Huntington's chorea are distinct and rather widespread, involving the frontorolandic cortex, the meninges, the vessels, the caudate nucleus and putamen, with an escape of the globus pallidus and the optic thalamus. It is worth noting at this point that despite the extensive cortical and striatal changes, no secondary degeneration was found in the pyramidal tracts or in the extra-pyramidal system. The fact that the caudate and putamen are selected in this disease with an escape of the globus pallidus is easily explainable when it is realized that the striatum is developed from the same part and is really one body separated in man by the passage of the anterior fibers of the internal capsule. As is well known, the globus pallidus is composed of large ganglion cells, which Malone has shown to be related to the motor system in their general structure. Some of these cells are scattered in the caudate and putamen, and they are relatively uninvolved. It is the small type of cell which bears the brunt of the pathologic process.

We were disappointed in the absence of pathologic findings in the case of acute chorea, especially so because Marie and Tretiakoff found such marked alterations in their case. Our case was undoubtedly one of Sydenham's chorea, the diagnosis being based on the type of irregular movement seen, the presence of endocarditis and eosinophilia. The case was not one of encephalitis, because the lesions of that disease were absent. We believe that in the course of Sydenham's chorea cerebral changes must occur, but modern methods have so far failed to

reveal them. Care must be taken in the interpretation of the various sections taken from the basal ganglions, because in control sections made from relatively normal persons the same cell changes were demonstrated as in the case of Sydenham's chorea. As Bielschowsky has shown, the collection of cells around the large motor type of ganglion cell in the corpus striatum will occur under normal conditions, an indication of the fragility of these elements. This was found in the case of Huntington's chorea, but not to a greater extent than in a normal case. There was no appreciable change in the smaller type of cell in the case of Sydenham's chorea, in the specimen of which the subthalamic region was normal and no cortical alterations were noted. The vessels were all markedly congested, but not more than is usual in a patient dying of pneumonia or any other infectious disease. No thrombosed vessels were found.

The symptomatology of the corpus striatum is being slowly evolved, due in large measure to the work by S. A. K. Wilson, Mills, C. and O. Vogt, Hunt, Spiller, Marie and others. It is worth noting that our knowledge of the functions of the corpus striatum has been derived largely from clinicopathologic study, and while our presentation is of small moment, it may add a little to the sum total of our knowledge.

SUMMARY

1. A clinicopathologic study was made of a case of Sydenham's chorea and of one of Huntington's chorea.

2. In the typical case of Sydenham's chorea a mitral endocarditis was found. The pathology in the brain of acute cell changes with the marked congestion can be attributed to the acute infectious disease from which the patient died.

3. In the case of chronic chorea the process involved mainly the striatum (caudate and putamen) and the cortex; the changes being typical of a chronic degenerative process in these parts, selective in action.

4. No relationship could be found between the acute and chronic varieties of chorea.

5. The findings of epidemic encephalitis were not present in our case of Sydenham's chorea. When such are present, as in Marie's case, we believe them to be the result of the epidemic forms of encephalitis and not ordinary types of acute chorea.

Charcot-Marie Atrophy: The Report of a Case with Necropsy

CHARLES S. POTTS, M.D.

AND

GEORGE WILSON, M.D.

PHILADELPHIA

CHARCOT-MARIE ATROPHY: THE REPORT OF A CASE WITH NECROPSY *

CHARLES S. POTTS, M.D., AND GEORGE WILSON, M.D.

PHILADELPHIA

Cases of Charcot-Marie atrophy with necropsy are sufficiently rare to warrant report. To date, six cases of this condition with the pathologic findings have been recorded; that reported by one of us (G. W.) is the only example from this country. The pathologic findings in the six cases have not been entirely uniform; all of them showed degeneration in the posterior columns, and in four of the six cases the peripheral nerves were diseased; in one slight degeneration was found in the peroneal nerves alone, and in one the nerve trunks were normal though the intramuscular filaments were altered. The anterior horn cells were greatly involved in one case, but the other five cases showed little alteration in the structure of these cells. Clark's columns were moderately affected in one case. The pyramidal tracts showed slight changes in two cases.

REPORT OF A CASE

Clinical History.—M. R., a single woman aged 51, was admitted to the Philadelphia General Hospital on July 9, 1914. At that time a note was made that a history could not be obtained because of the mental condition of the patient. In 1918, the history of M. R. which follows was obtained from her mother: The father died from unknown cause at the age of 38. The patient is one of five living children, aged respectively 60, 58, 57, 51 and 48 years. One child died in spasms when 18 months old and the mother had one miscarriage. No member of the family had had symptoms similar to those of the patient. She had the usual diseases of childhood, was bright, and received a common school education. As a child her legs were weak and she had to be helped up and down stairs by members of the family. She assisted with the housework but was never employed outside the home. Two years before going to the hospital she became bedridden and apparently suffered severe pain.

On July 26, 1918, one of us (C. S. P.) examined the patient and found: The woman was deficient mentally and unable to give a history of her illness. Vision appeared to be good and the cranial nerve functions were normal with the exception that a moderate degree of deafness was present. The pupils were contracted, irregular, and did not react to light, but reacted well in accommodation. The eyegrounds were normal. The patient was unable to walk or to feed herself. All movements of the arms could be made, though with diminished strength, but there was very little movement of the hands or fingers.

Hyperextension was present at the metacarpophalangeal joint of all fingers except the index fingers; the second and third joints of all the fingers were flexed. The fingers, with the exception of the little and ring fingers of the left hand, could be passively straightened. The muscles of the shoulder girdle and arms were slightly atrophied; atrophy was much more intense below than above the elbows and fibrillary twitchings were present in the muscles of the forearms. The muscles of the back were well developed. Slight
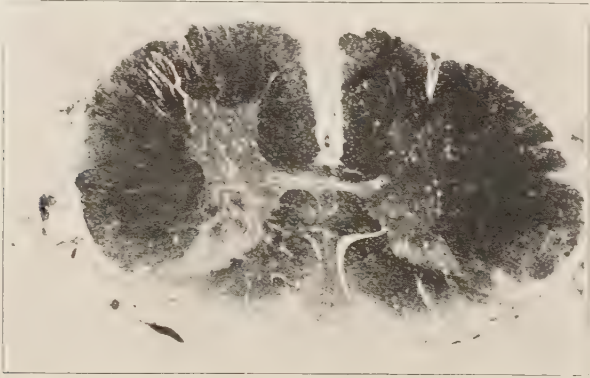
Fig. 1.—Section of the second lumbar segment of the spinal cord.
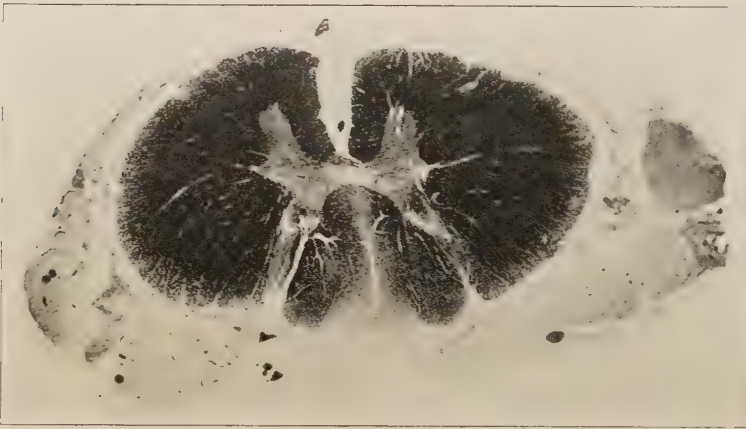
Fig. 2.—Section of the cord from the mid-dorsal region.

power was present in the muscles of the legs, but was practically absent in those of the feet. The thighs were flexed on the abdomen and the legs on the thighs; the knees were ankylosed in a state of semi-flexion, and the feet were in the position of talipes cavus with slight varus. Atrophy and fibrillary twitchings were present in the muscles of the legs, especially in the peroneal and anterior tibial muscles. The patellar and achilles reflexes were absent and plantar stimulation produced flexion on both sides. Incontinence of urine was present, possibly in part due to the patient's mental condition, and in
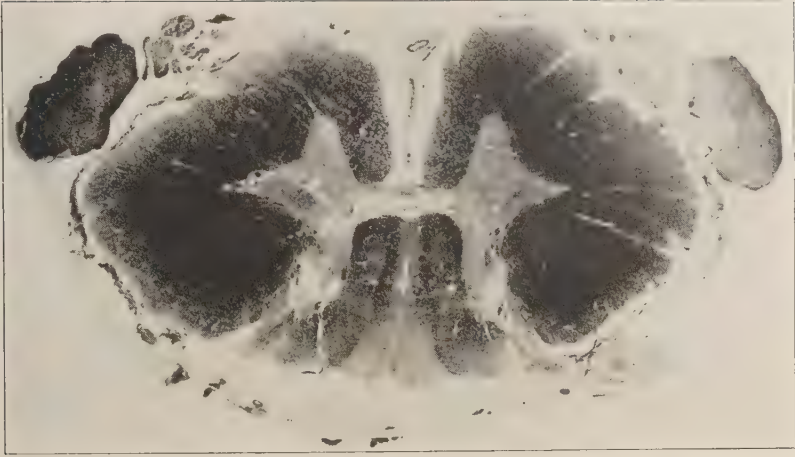
Fig. 3.—Section of the first dorsal segment of the cord.
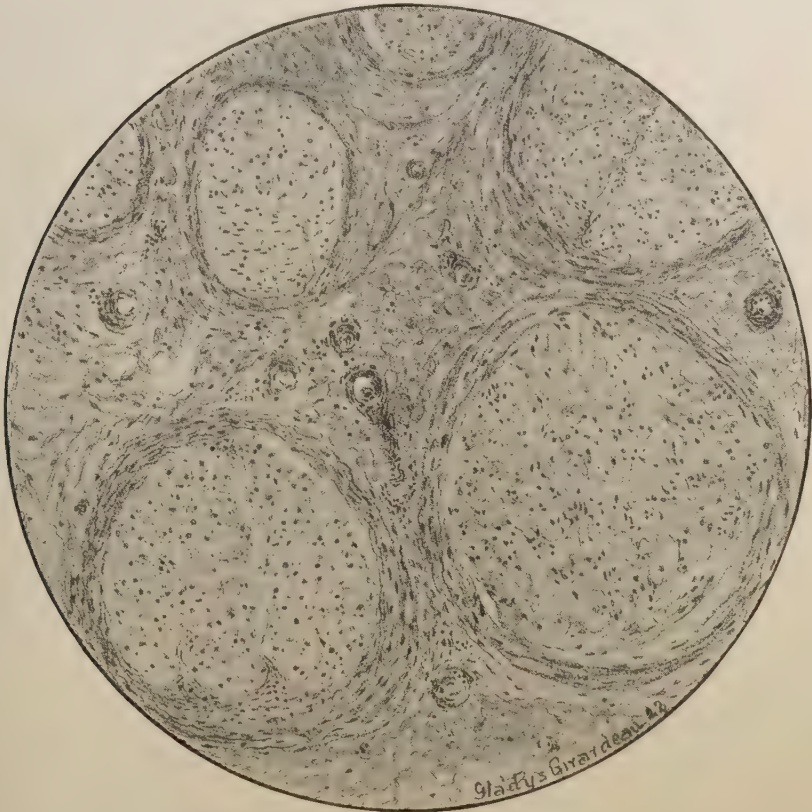
Fig. 4.—Low power drawing of the ulnar nerve.

part to lack of team work between the patient and the attendants. She apparently perceived painful stimuli but other forms of sensation could not be tested owing to lack of cooperation. None of the muscles of the legs, forearms and hands reacted to the faradic current. The Wassermann reaction with both blood and spinal fluid was negative, and no cells were found in the fluid. The patient died May 24, 1920, as the result of broncho-pneumonia.
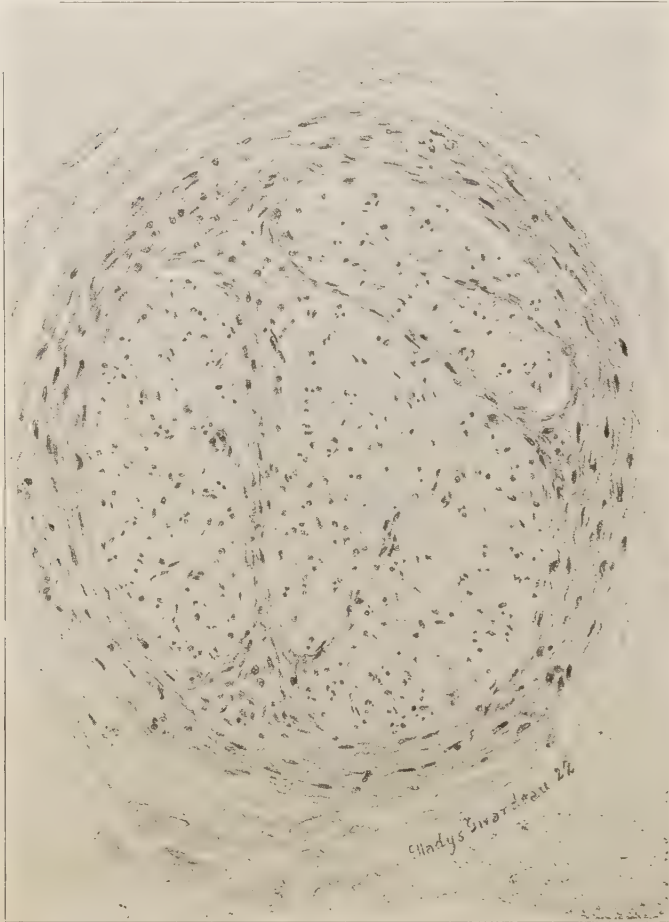
Fig. 5.—High power drawing of the ulnar nerve.

Pathologic Study of the Nervous System.—The spinal cord and the posterior and anterior roots appeared small on gross examination. The meninges, the cells of Clark's columns, and the pyramidal tracts were normal. The anterior horn cells in the lumbar, sacral and cervical regions were diminished in size and number; the nuclei were eccentric, the cell bodies stained poorly and consisted chiefly of a granular material. The changes in the anterior horn cells were most marked in those segments concerned with the muscles of the feet, legs, hands and forearms. In the upper cervical and upper lumbar regions the

cells of the anterior horns were altered but not so severely as those already described. The posterior columns were moderately degenerated throughout all regions of the cord. The degeneration was usually confined to the region about the posterior septum, but in the cervical levels, Burdach's columns were also involved. Lissauer's zones were greatly sclerosed in the sacral, lumbar and cervical regions. The cerebrum showed no changes of note.

The plantar, peroneal, median and ulnar nerves were degenerated, the plantar and peroneal nerves being intensely involved. The plantar nerves contained few healthy fibers; the median and ulnar showed a reduction in the number of healthy fibers but not to the severe degree observed in the plantar and peroneal nerves. The perineurium was greatly thickened in all the nerves examined; the epineurium showed slight hypertrophy, and the endoneurium was not appreciably altered.

Tissue removed from the plantar surface of the foot, and from the thenar and hypothenar eminences showed practically no muscle tissue at all; fat and connective tissue were the only structures present.

COMMENT

The pathologic changes in our case therefore corresponded with the two findings most commonly reported in cases of Charcot-Marie atrophy in which necropsies have been recorded: degeneration of the peripheral nerves and of the posterior columns of the cord. The cells of the anterior horns were more involved in this case than in the one reported by Wilson in 1918.

Clinically, our case showed the presence of mental changes and Argyll-Robertson pupils; these have occasionally been observed in other cases of peroneal muscular atrophy. Indeed, a number of cases have been reported with such atypical manifestations as increased reflexes, Babinski's sign, optic atrophy, ocular palsies and bulbar symptoms. The occasional appearance of these unusual symptoms in Charcot-Marie atrophy may be explained on the ground that hereditary diseases of the nervous system are, at times, blended together; hence atypical findings are to be expected.

P. GAUDISSART

Hypercholestérinémie

ET

Rétinite albuminurique

HYPERCHOLESTÉRINÉMIE ET RÉTINITE ALBUMINURIQUE

par P. Gaudissart

(Travail fait au Départemeut de Pathologie du "Philadelphia General Hospital", Philadelphie, E.-U.)

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Peu d'affections oculaires ont une pathogénie aussi discutée que la réti-nite albuminurique.

Sans avoir l'intention de passer en revue la volumineuse littérature de cette question, rappelons brièvement que la production des lésions réti-niennes fut diversement attribuée à l'hypertension sanguine, à des lésions vasculaires et à des modifications chimiques de la composition du sang, notamment à la rétention d'urée.

Dans ces dernières années, l'attention des cliniciens en médecine interne s'est portée sur les modifications de la teneur du sang en lipoïdes, plus spécialement en cholestérine, dans diverses affections parmi lesquelles la néphrite.

La notion de la cholestérine fut introduite en ophtalmologie par Chauf-fard et par ses collaborateurs. Il attribua d'abord à l'hypercholestérinémie la genèse du gérontoxon, du xantélasma et, plus tard, du synchisis scin-tillant.

Le mécanisme de la production de ces lésions, comme de celles de la réti-nite albuminurique, dont nous allons parler bientôt, comprendrait deux stades :

Un premier, pendant lequel il y aurait simplement une augmentation de la quantité de cholestérine du sang : stade de la cholestérine circulante.

Au second stade, ou stade de la cholestérine fixée, se formeraient des dépôts locaux dans la peau des paupières (xantélasma), la cornée (géron-toxon), le vitré (synchisis scintillant).

En 1911-1912, Chauffard présente 14 cas de rétinite albuminurique avec hypercholestérinémie à laquelle il attribue la formation des exsudats blancs rétiniens. Pour lui, au niveau d'un exsudat primitivement fibrineux se dépo-serait ultérieurement la cholestérine, et cela grâce à l'excès de cholestérine du sang.

L'hypercholestérinémie serait un phénomène précoce de la néphrite et diminuerait ultérieurement, sans disparaître cependant, au fur et à mesure des progrès de l'urémie et de l'intoxication sanguine.

C'est donc au stade de début des rétinites que devraient se trouver les hypercholestérinémies les plus fortes.

Achard et Feuillé, Chauffard, G. Laroche et Grigaut, dans des mémoires successifs, confirmèrent ces premières données.

Laroche, Grigaut et Chauffard, en 1920, publièrent un tableau de 28 cas de rétinite albuminurique, toutes avec augmentation de la cholestérine, de l'urée, de la pression sanguine.

Mais la question de la pathogénie de la rétinite albuminurique est double : elle comprend d'abord l'étude des modifications de la composition du sang au moment de la production des lésions, ensuite l'examen histochimique des rétines elles-mêmes. Ces deux méthodes se complètent mutuellement.

La seconde, plus que la première, permettrait d'arriver à des certitudes, n'était l'imperfection de nos connaissances histochimiques.

Déjà, en 1909, antérieurement donc aux travaux dont nous venons de parler, Laubert et Adamüch affirmèrent que les taches blanches de la réti-nite albuminurique présentaient les réactions caractéristiques des lipoïdes, c'est-à-dire la double réfraction en lumière polarisée, la coloration noire par l'acide osmique, orangé par le Soudan III, rose par le Nilblau.
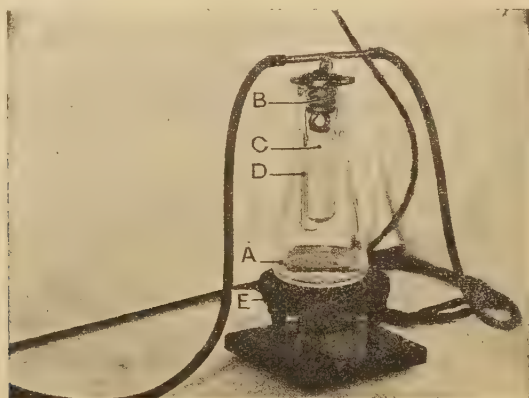
Fig. 1. — A, chloroforme bouillant; B, serpentin condensant les vapeurs de chloroforme dans C, récipient de carton filtre cgntenant 1 cmc de sang mêlé à 4 gr. de plâtre de Paris ; D, siphon vidant le récipient C, des dès que le chloroforme atteint un certain niveau ; E, four électrique.

En 1912, Chauffard, Guy Laroche et Fontréaulx, par l'étude microsco-pique d'une rétine étalée à plat et dont le possesseur avait présenté une rétinite albuminurique et de l'hypercholestérinémie, arrivèrent aux mêmes conclusions.

La même année, Ginsberg, par des méthodes analogues, obtient des résultats identiques quoique moins affirmatifs. Il n'a pu établir très bien l'importance respective des cellules à lipoïdes et des lipoïdes extracellu-laires. « Les cellules à lipoïdes, dit-il, sont très petites et n'existent pas en couches assez épaisses pour être visibles ophtalmoscopiquement. Les taches blanches de la rétine sont d'origine multiple, origine qui ne peut être déter-minée par l'examen ophtalmoscopique. »

Mawas, en 1913-1916, reprend l'étude histologique de la rétinite albumi-nurique au point de vue qui nous occupe et arrive à des conclusions tout à fait opposées.

Quatre lésions, écrit-il, produisent les changements ophtalmoscopiques de la rétinite albuminurique.

La lésion initiale, la plus fréquente et la plus importante, est un exsudat fibrineux dans la couche intergranulaire et dans la couche granuleuse externe de la rétine. Ultérieurement, et dans certains cas, cette exsudation

fibrineuse est phagocytée par des cellules granuleuses. Ces dernières, qui se retrouvent d'ailleurs dans beaucoup de lésions de dégénérescence des fibres nerveuses, sont de grosses cellules rondes à petit noyau, dans le protoplasme desquelles ont été mises en évidence, par les procédés spéciaux dont nous avons parlé plus haut, des gouttelettes de lipoïdes. Les lipoïdes que possèdent ces cellules leur appartiennent en propre et ne proviennent pas des exsudats phagocytés. En effet, Mawas n'a jamais réussi à trouver des lipoïdes dans ces exsudats. Les agglomérations de ces cellules granuleuses spéciales constituent les seules plaques blanches lipoïdiques de la rétinite albuminurique. Elles doivent être considérées comme un phénomène tardif et tout à fait passager au cours de cette affection. Cette conclusion est en contradiction absolue avec les idées de Chauffard pour qui le dépôt de cholestérine constitue le phénomène initial et primordial de la rétinite.

La troisième lésion rétinienne est un décollement de la membrane limitante interne, donnant ophtalmoscopiquement l'aspect de grandes taches opalescentes.

Enfin, des dégénérescences gangliformes de la couche des fibres nerveuses apparaissent parfois à l'optalmoscope comme de petites taches blanches.

Ces deux dernières lésions sont rares et peu importantes.

Comme on le voit, les recherches histologiques n'ont guère contribué à résoudre le problème.

Nous avions entrepris ce travail dans le but de reprendre les recherches de Chauffard à un point de vue plus ophtalmoscopique, dans l'intention de déterminer notamment les relations entre l'hypercholestérinémie et les différentes formes d'exsudats rétiniens, de saisir la coïncidence entre l'apparition des premières taches blanches et l'augmentation du taux de la cholestérine. Nos recherches nous ont donné des résultats très différents de ceux que nous attendions.

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MÉTHODES. — Nous avons adopté pour le dosage de la cholestérine la méthode colorimétrique décrite en 1918 par Myers et Wardell.

Nous renvoyons pour les détails techniques au mémoire original de ces auteurs. Résumons cependant brièvement cette méthode :

Un centimètre cube de sang est intimement mélangé à 4 gr. environ de plâtre de Paris. Ce mélange est séché par un séjour d'une heure à l'étuve à 90° et la cholstérine qu'il contient extraite par le chloroforme bouillant.

L'extrait ainsi obtenu et une solution chloroformique de cholestérine d'une concentration connue sont soumis à la réaction colorante de Liebermann-Burchard (anhydride acétique et acide sulfurique), laquelle, en présence de cholestérine, donne une belle couleur bleu vert, d'autant plus intense que la concentration est plus grande. Les deux solutions sont mises au colorimètre et leur teneur comparative en cholestérine déterminée.

Nous avons adopté cette méthode parce qu'elle est relativement plus simple que les méthodes gravimétriques, tout en donnant cependant des résultats cliniquement exacts. Les tests auxquels ses auteurs l'ont soumise en la comparant avec les méthodes gravimétriques de Windhaus et à la

digitanine ont prouvé sa valeur. On en trouvera les détails dans l'article original.

Nous nous sommes fréquemment assuré que l'extraction de la cholestérine était totale en soumettant à la réaction colorante le dernier chloroforme d'extraction et en constatant qu'il restait incolore.

Nous n'avons jamais obtenu la moindre trace de coloration après une demi-heure d'extraction.

Nous avons opéré sur le sang total recueilli en tubes oxalatés. La quantité de cholestérine du sang total est un peu moins considérable que celle du sérum. Selon Myers, le sang humain normal renferme de 130 à 170 milligr. de cholestérine pour 100 cc.

Dans le but de vérifier cette assertion, et aussi pour déterminer l'influence du facteur personnel nous avons entrepris une série de dosages sur des sangs de malades atteintsd'affections non susceptibles de modifier la teneur du sang en cholestérine.

Tableau I. — Contrôle

DIAGNOSTIC CLINIQUE	CHOLESTÉRINE milligr. pour 100 c. c.
1. Choroïdite centrale	140
2. Thrombose branche veine centrale	155
3. Kérato-conjonctivite phlycténulaire	120
4. Atrophie toxique faisceau maculaire. . . .	166
5. Urétrite gonococcique chronique	150
6. — — —	150
7. — — —	145
8. — — —	170
9. — — —	155
10. Chancre induré	160

Le tableau I montre que sur 10 de ces échantillons, le chiffre le plus bas est de 120 milligr., le plus élevé 170 milligr. Aussi nous croyons-nous autorisé à considérer comme hypercholestérinémique tout sang dont la teneur en cholestérine dépasse 170 milligr. par 100 cc.

Le dosage de l'urée fut effectué par la méthode à l'uréase, également sur le sang total. Les chiffres de nos tableaux donnent la teneur du sang en urée, non en azote.

Ajoutons enfin que nous n'avons pas choisi nos rétinites, mais retenu toutes celles qui sont tombées sous notre observation dans les cliniques et hôpitaux de Philadelphie pendant le temps que nous avons consacré à ce travail.

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RÉSULTATS. — Nous avons divisé nos cas en trois catégories que nous exposons en trois tableaux.

Le premier comprend les néphrites avec hypercholestérinémie et sans rétinite, le second les cas de rétinite albuminurique sans, le troisième avec hpercholestérinémie.

Nous pouvons envisager de trois façons les rapports possibles de l'hypercholestérinémie et de la rétinite albuminurique :

Ou bien la cholestérine serait la cause directe de la rétinite, son excès dans le sang produisant, par dépôt au niveau des exsudats fibrineux rétiniens, les soi-disant taches blanches caractéristiques de cette affection ;

Ou bien les deux phénomènes, rétinite et hypercholestérinémie, coïncident sans cependant que l'un soit la cause de l'autre, ces deux symptômes étant les manifestations d'un même état morbide, le résultat d'une même cause pathologique : la cholestérine serait en quelque sorte le témoin de la rétinite ;

Enfin, troisième hypothèse, il n'y aurait entre les deux aucun rapport.

Un premier regard jeté sur nos tableaux II et III montre que, sur nos 18 rétinites, 11 ne présentent pas, 7 présentent de l'hypercholestérinémie.

Tableau II. — Rétinite albuminurique sans hypercholestérinémie

DESCRIPTION OPHTALMOSCOPIQUE	TENSION SANGUINE		URÉE milligr. pour 100 c. c.	CHOLESTÉRINE milligr. pour 100 c. c.
	Diastole	Systole		
1. Œdème rétine et papille, hémorragie, exsudates gris sales.	165	215	56	150
2. Œdème rétinien, hémorragies, exsudats œdémateux .	120	260	62	130
3. Œdème papillaire et rétinien, exsudats blanc-jaunâtres, hémorragies	135	290	47	125
4. Névro-rétinite, hémorragies, exsudats blancs, étoile maculaire partielle	140	235	46	130
5. O. D. Obstruction artère centrale ancienne. — O. G. Œdème et stase papillaire, exsudats blancs, étoile maculaire partielle, hémorragies	n'a pu être obtenue		94	140
6. Œdème rétinien et papillaire, petites hémorragies, exsudats ponctués gris, gris-jaunes et blancs . . .	120	150	73	140
7. Exsudats blancs, petits, dans le voisinage de la papille.	130	200	"	115
8. Rétinite ancienne, artériosclérose prononcée, hémorragies, exsudats gris sale	80	160	80	160
9. Œdème rétinien et papillaire, petites hémorragies, exsudats blanc-jaunâtres exsudats œdémateux . .	110	205	77	150
10. Œdème rétinien et papillaire, hémorragies, exsudats blanc-jaunâtres	110	200	47	160
11. Œdème papillaire et rétinien, hémorragies, petits exsudats jaunâtres	115	170	280	145

Tableau III. — Rétinite albuminurique avec hypercholestérinémie

EXAMEN OPHTALMOSCOPIQUE	TENSION SANGUINE		URÉE milligr. pour 100 c. c.	CHOLESTÉRINE milligr. pour 100 c. c.
	Diastole	Systole		
1. Œdème de la papille et de la rétine, exsudats jaunâtres, lésions vasculaires	145	220	88	232
2. Œdème rétinien, hémorragies, exsudats blancs. . . .	200	260	68	240
3. Œdème rétino-papillaire hémorragies, exsudats blancs.	160	260	24	175
4. Œdème rétino-papillaire, hémorragies, exsudats blancs, étoile maculaire	120	270	193	180
5. Nombreuses hémorragies, exsudats blancs et jaunes synchisis scintillant	140	205	75	220
6. Œdème rétinien et papillaire, exsudats blanc-jaunâtres, petits, entourant la papille	85	170	60	220
7. Névro-rétinite ancienne, exsudats jaunes, artério-sclérose des vaisseaux	200	260	20	180

Parmi les rétinites de notre tableau II, les cas 3, 7, 6, 8, 10 sont des cas de début, tant par l'histoire clinique des malades dont le trouble visuel était tout récent que par l'aspect de la rétine. Ces malades, bien que présentant les taches blanches rétiniennes caractéristiques, ont une cholestérinémie normale. Le cas 6 du même tableau est particulièrement intéressant, car nous en avons pu suivre très exactement l'évolution : à notre premier examen, le fond de l'œil présentait un œdème de la papille et des régions environnantes de la rétine avec quelques petits exsudats, les uns gris, se détachant à peine sur le fond rétinien, d'autres plus clairs, certains enfin d'un blanc éclatant ; quelques semaines plus tard, un exsudat plus grand et blanc brillant s'était formé au voisinage de la papille ; malgré cette formation d'exsudats à laquelle nous assistions ophtalmoscopiquement, la teneur du sang en cholestérine était normale : 140.

Le cas 10 tableau II nous permit la même observation : un premier examen ophtalmoscopique nous révéla une neuro-rétinite débutante, sans exsudats ; quatre semaines après, nous constatons un exsudat blanc-jaunâtre assez étendu, le long du bord papillaire. Chez ce malade, atteint d'une rétinite en pleine formation, la quantité de cholestérine du sang était normale (160 la première comme la seconde fois). Les autres cas de notre tableau II, malgré la présence de rétinites en pleine évolution et typiques (deux montraient une étoile maculaire), ne présentent pas d'hypercholestérinémie. Dans ces conditions, il nous semble bien difficile d'attribuer à la cholestérine e rôle essentiel et primordial dans la formation de l'exsudat de la rétinite albuminurique.

Nous croyons d'ailleurs que c'est une erreur de parler d'un exsudat caractéristique de cette affection. Entre les taches gris-sales, d'aspect œdémateux, et les plaques d'un blanc brillant nous avons trouvé tous les intermédiaires. De plus, des aspects ophtalmoscopiques considérés comme typiques, tels que l'étoile maculaire, se retrouvent parfois dans des affections très différentes comme l'érysipèle, la syphilis, la papille de stase. Il est plus

probable que la rétine réagit de façon identique à des excitations patholo-
giques diverses, tout comme de multiples infections de la conjonctive pro
duisent des fausses membranes.

Nous avons envisagé l'hypothèse où l'hypercholestérinémie, sans être la
cause de la rétinite, apparaîtrait en même temps qu'elle. Cela nous semble
peu probable. Sur nos 18 cas de rétinite, 7 seulement présentent de l'hyper-
cholestérinémie, mais ont en même temps une urémie plus ou moins pro-
noncée ou une tension sanguine élevée.

D'autre part notre tableau IV montre 8 néphrites chroniques sans rétinite,
bien que la quantité de cholestérine dans le sang soit supérieure à la nor-
male parfois d'une façon considérable. Nous avons trouvé ces 8 néphrites
hypercholestérinémiques en opérant sur un nombre environ double de cas.
Il nous eût été facile d'en trouver un nombre beaucoup plus élevé, mais
nous croyons que notre tableau suffit pour démontrer que, dans la néphrite
chronique, une hypercholestérinémie élevée est compatible avec l'absence
de rétinite.

Tableau IV. — Néphrites avec hypercholestérinémie et sans rétinite

DIAGNOSTIC CLINIQUE	TENSION SANGUINE		URÉE milligr. pour 100 c. c.	CHOLESTÉRINE milligr. pour 100 c. c.
	Diastole mm.	Systole mm.		
1. Néphrite chronique	90	150	42	220
2. — —	70	130	27	420
3. — —	75	115	24	292
4. — —	1·10	210	103	192
5. — —	80	140	183	170
6. — —	20	125	75	180
7. — —	90	180	120	230
8. — —	140	230	94	190

Nous nous trouvons ainsi amené à notre troisième hypothèse : *Puisque
de nombreux cas — plus de la moitié — de rétinites albuminuriques ne
présentent pas d'hypercholestérinémie et que celles qui en présentent ont
en même temps soit de l'urémie, soit une tension sanguine élevée et puis-
que, d'autre part, il existe des néphrites chroniques avec hypercholesté-
rinémie et sans rétinite, il ne nous semble pas exister de rapport bien défini
entre la rétinite albuminurique et l'hypercholestérinémie.*

Nous n'envisagerons pas ici la pathogénie de la rétinite albuminurique
d'autres points de vue. Contentons-nous de faire observer quelques coïnci-
dences intéressantes, sans en exagérer l'importance ni la nouveauté.

Tous nos cas de rétinite, sans exception, présentent soit une tension
sanguine élevée, soit une augmentation du taux de l'urée. Il ne faut pas
cependant attribuer à nos chiffres une valeur trop absolue, ces deux élé-
ments étant influencés par le repos, le régime, etc. De plus, un certain

nombre de nos cas à tension normale ou subnormale sont en état de décompensation cardiaque et ont par conséquent fait de l'hypertension à un moment de leur évolution.

Il nous semble pourtant intéressant de constater que, sur nos 18 cas de rétinite, 13 ont une hypertension marquée (200 ou au delà) et, sur nos 8 néphrites sans rétinite, 2 seulement possèdent une tension sanguine au-dessus de la normale alors que 5 ont une urémie plus ou moins marquée. Enfin 12 de nos malades atteints de rétinite avaient une urémie supérieure à 50 milligr. pour 100 cc.

* * *

Conclusions. — 1° L'hypercholestérinémie ne semble pas jouer un rôle bien défini dans la genèse des exsudats de la rétinite albuminurique ;

2° Il ne paraît pas y avoir de rapport de coïncidence entre l'hypercholestérinémie et la rétinite albuminurique ;

3° L'hypertension sanguine et la rétention d'urée, soit isolément, soit réunies, accompagnent presque invariablement la rétinite albuminurique.

En terminant ce travail, nous tenons à remercier Dr. Edward B. Krumbhaar, directeur du département de Pathologie du « Philadelphia General Hospital » de la généreuse hospitalité qu'il nous a offerte dans ses magnifiques laboratoires. Les conseils du Dr W. H. Stoner, du laboratoire de Biochimie du même département, nous ont été très utiles pour l'exécution de la partie technique de nos recherches. Nous lui exprimons ici tous nos remerciements.

Philadelphie, 30 juillet 1921.

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TROPICAL INGUINAL GRANULOMA IN THE EASTERN UNITED STATES[1]

ALEXANDER RANDALL, JAMES C. SMALL AND WM. P. BELK

Philadelphia, Pennsylvania

We wish in a preliminary report to briefly call your attention to a condition supposedly occurring only in the tropics, and its endemic existence in the temperate parts of the eastern United States.

Under the following variety of names: tropical inguinal granuloma, tropical ulcer, venereal granuloma, granuloma inguinale, and granuloma pudendi, there has long been recognized by physicians practising in the tropics and especially in South America a disease which was supposedly limited to these countries.

Last year Symmers and Frost reported from the laboratories of the Bellevue Hospital, New York, two cases of tropical inguinal granuloma found in negroes of that city, and this number has recently been augmented in a later report by Campbell of three further cases found in the urological wards of that institution.

Recognizing the similarity of the lesions, as illustrated by Symmers and Frost, to certain cases that have been repeatedly seen on the urological service of the Philadelphia General Hospital, a round-up was instituted on commencing the service January 1 with the result that 5 men and 2 women were found, in the institution suffering from this condition. These numbers have been increased since that time by 3 men and one woman patient, making a total of 11 cases under observation. Four further cases have been reported to us: one an inmate of the Penitentiary who had on two previous occasions been treated

[1] Read before the American Association of Genito-Urinary Surgeons, May 3, 1921, Richmond, Va.

for this condition at the Philadelphia General Hospital; a second and a third, observed by Dr. A. H. Lippincott of Camden, New Jersey, after being diagnosed by our laboratory; and a fourth, a native of New Jersey who is awaiting hospital admission having been referred by Dr. J. L. Herman: a total of 15 cases.

The first and most important fact, when making such a diagnosis of a supposedly tropical disease as present in the temperate zone, is the unquestioned accuracy of the diagnosis. We have turned to the work of Aragao and Vianna of Rio Janeiro, who are probably the world's authorities on this condition, and the originators of the specific antimony treatment, and we have been able to corroborate and substantiate in our cases all the bacteriological data that they report, while the result of the specific treatment, and the similarity of the appearance of the lesions, as we have seen them, to the splendid photographic and colored illustrations in their work have alone been almost self-substantiating.

This disease has been present, practically constantly, in the Philadelphia General Hospital as long as any of the attending physicians and nurses can remember. It has masqueraded both here as elsewhere, under various other diagnoses, among which may be mentioned lues, now ruled out as in fact it has always been, by the repeatedly negative blood tests, lack of specific history and absolutely negative results with arsenic therapy; as chancroidal infection, to which it rarely bears any similarity as destructive ulceration is particularly not a characteristic; as tuberculosis, though never substantiated by microscopic study; as condylomata, to which when seen in the female or about the anal region it bears a close similarity; and as carcinoma, to which the microscopic picture in two of our cases was almost typical.

HISTOLOGICAL RECORD OF INGUINAL GRANULOMA[2]

Four cases: 2, 11, 6, 7. Tissues were fixed twenty-four hours in formalin; sections were cut from paraffin blocks and stained with hematoxylin and eosin.

[2] By Dr. William P. Belk.

The general appearance of the four was the same. There was a proliferation of fibrous tissue, moderate in amount, and enormous numbers of polymorphonuclear leucocytes and endothelial cells. Some times one, sometimes the other predominated. The vessel walls were somewhat thickened, as in chronic inflammatory processes. There was in every case some proliferation of the squamous epithelial cells of the skin; in no. 7 this was quite marked, and in no. 6 proliferation was so marked and extended so deeply that a preliminary diagnosis of epithelioma was made. There was in some cases, slight amount of necrosis, but this was never marked, nor was abscess formation noted. The process was separated from normal tissue by bands of connective tissue.

Sections from two rabbits autopsied. Rabbit 3 and rabbit 5 showed identical histological pictures. In these cases, the infecting organism was stained in the tissues by the following method: six hours fixation in Sheuder's solution, 1 hour in Giemsa stain, otherwise technique as ordinarily recommended for Giemsa.

BACTERIOLOGICAL METHODS AND LABORATORY DIAGNOSIS[3]

Direct smears

Direct smears from the lesions, properly prepared and stained, constitute a very reliable method of diagnosis. The material may be collected on sterile cotton applicators for either the smears or the cultures. Thin spreads of this material are essential. These are dried quickly in air and stained either by Wright's, or Geimsa's stain. Wright's method is the more rapid and has given satisfactory results. The most difficult part of the procedure is to obtain the proper differentiation of the stained smear in distilled water. Even with the most intense Wright's staining this differentiation should not be carried on for more than fifteen or twenty seconds. Application of the water for too long entirely decolorizes the capsules of the organisms: for too short a period, the capsules appear blue and the morphology of the bodies of the organisms cannot be observed clearly. With the best staining results, the organisms appear as small rounded pink bodies with a dark blue coccoid body in the center; or, more frequently, as oval pink bodies with a bacillary, or diplococcoid body occupying the longitudinal axis. The pink outer zone is a wide bacillary capsule; the dark blue central bodies represent metachromatic granules within

[3] By Dr. James C. Small.

the bacillary body proper. The true outline of the bacillary body can be seen only after the capsule has been entirely decolorized by differentiating with distilled water. In stained smears from the lesions, some areas show organisms with capsules stained pale blue and obscurely differentiated central bodies; other areas show well defined dark blue metachromatic granules surrounded by a pink capsule, which latter, however, obscures the outline of the bacillus proper; and still other areas are seen in which the capsules have been entirely unstained and where the organisms appear as short, thick bacilli with rounded blunt ends occupied by the dark blue metachromatic granules. The organisms thus present a true bipolar-stained appearance with the intervening body shaft of the bacillus stained a pale blue. Always a few bacilli, shorter than those just described, stain solidly a deep blue.

The organisms are found within the cytoplasm of large mononuculear cells. In such they have well defined capsules, or may appear as nests. of bacteria occupying a rounded area within the cell and revealing no capsules. In such nests the bipolar staining may be observed. The polymorphonuclear leucocytes do not contain encapsulated forms. Encapsulated forms may appear free, or in relation to cellular detritus. In the latter instances they occur chiefly in groups and in the neighborhood of large naked mononuclears. These presumably represent organisms released from the disintegrated cytoplasm of mononuclear cells. In the former instances they may occur singly and in no relation to cellular detritus.

Smears from the lesions are remarkaby sparse in bacteria, as compared with smear preparations from other types of ulcerative lesions about the genitalia. Staphylococci, streptococci, diphtheroid bacilli and bacilli having the morphology and staining character of the colon group have been observed widely scattered, or in small clumps within the polymorphonuclear cells.

Cultures

The granuloma organisms have been grown in cultures in four instances. Of the various media and methods tried, surface inoculation of Sabaraud's maltose agar (2 per cent acid), as recommended by Aragao and Vianna, proved the most useful. This degree of acidity tends to inhibit some of the contaminating bacteria, and permits profuse growth of the granuloma bacillus. The growth is quite characteristic after twenty-four hours incubation. Colonies appear slightly gray white,

moist, glistening, dome shaped on round regular basis from 1 to 3 mm. in diameter. When touched with an inoculating wire they appear quite viscid and have the consistence and appearance of thin starch paste. By transmitted light they are translucent and have a slight brownish tinge. They are usually the largest colony appearing in these mixed cultures of the material taken directly from the lesions, and are very readily recognized.

In subcultures growth occurs on all of the simpler media. Enriched media is not necessary, on semisolid media the character of the growths does not differ essentially from that described above. In fluid media there is diffuse turbidity with a surface ring tending to adhere to the sides of the culture tube and to climb slightly above the level of the liquid. Later sedimentation occurs. Growth is profuse even in 1 per cent peptone water. In litmus milk there is acid production and coagulation within twenty-four hours. On potato growth is profuse, moist and sightly brownish in color. There is a decided blackening of the potato.

Smears from cultures, when stained with Wright's stain, show essentially the morphologic details previously described; in smears from Sabaraud's media and from moist glucose or plain agar, wide capsules are readily demonstrated, so that the organisms appear as do the encapsulated ones in direct smears from the lesions. In smears from broth cultures, capsules are not demonstrated, so that the organisms from twenty-four hour old cultures appear as short, plump bacilli exhibiting irregular staining—for the most part showing a dark area at either pole with pale blue intervening. In older cultures, especially in media containing a carbohydrate which has been fermented with decided acid production, long forms occur. These forms also stain irregularly, presenting dark blue banded areas, alternating with pale blue areas throughout the length of the organism.

Our study of the organism may be tabulated briefly:

Non-motile, non-sporulent, encapsulated bacillus, Gram negative; showing metachromatic granules as well as capsules with Romanowski staining.

It does not liquefy gelatin, or coagulated serum.

It hemolyzes blood in agar plates.

It does not form indol.

Coagulates and acidifies milk within twenty-four hours.

It ferments dextrose, levulose, lactose, galactose, saccharose, malatose, arabinose, mannitol, salicin, inulin, and dextrin. It does not ferment dulcitol and rice starch.

Pathogenicity

Intraperitoneal inoculation kills white mice and guinea pigs in twenty-four to forty-eight hours. The organisms are recovered at autopsy from the peritoneal fluid, the blood and the various internal organs.

Cutaneous inoculations of white mice, guinea pigs, rabbits, cats and dogs all failed to produce definite lesions.

Intradermal inoculations of dogs were also negative.

Subcutaneous inoculation of white mice and guinea pigs produced an inflammatory reaction, going on to abscess formation in some instances but always with spontaneous and rapid healing. In dogs and cats no abscess formation occurred, only a slight inflammatory reaction being noted.

In rabbits it produced large subcutaneous infiltrations with abscess formation and spontaneous rupture producing ulcers some of which have failed to heal after an observation period of six weeks.

CLINICAL STUDY

Symptoms

The usual history is that the lesion started as a small papule, non-inflammatory, which after rupture and the exudation of a slightly purulent fluid, refused to heal, and exhibited progressive tendencies toward slow proliferation and spreading. The lesion in its purity (especially seen when involving the inguinal region), is a flesh-red, exuberant, overgrowth of soft granulation tissue. It has absolutely no simularity to an ulcer, with its eroding, undermining, necrotic base. The center of the granuloma appears slightly depressed, and there is certainly a destructive action present, but the edges are redundant and overlap the apparently healthy skin margin. Exudate is scant, mucoid in character, of a non-offensive odor, and when wiped with gauze is easily removed, leaving a clean blood-red surface, similar in every respect to a large area of healthy granulation tissue as seen in clean surgical wounds. This picture varies according to the duration, size and location. The older lesions show at times tendencies towards cicatrization at some points, while spreading in others, but this only occurs when flat non-

chafing surfaces are involved. Large lesions, especially those in the perineum, become bulbous, simulating condylomata acuminata, with large rounded heads of new growth, the heads ofttimes with pearly white surfaces of epithelization, and deep crypts with raw granulomatous surfaces. Secondary infection here causes the clean, odorless character to change.

As indicated by the name the most frequent location is in the groin spreading upward as far as the anterior superior spine and downward through the fold of the groin frequently involving the perineum, and in some cases following the fold of the nates and spreading to the buttocks. Prepucial lesions are likewise frequently associated and at times primary, and involvement here has given us the most destructive picture with a gradual erosion of the glans and even the shaft of the organ. In the female, the labia majora share the brunt of the attack with the perineum and groin involvement in some cases. We have had one case, a male, with the granuloma limited to a proliferative growth about the anus.

The patient has few subjective symptoms. They suffer no pain or discomfort unless the involved areas are so placed as to cause chafing. The granuloma is practically painless to the touch, and only deep pinching-up of the mass will cause suffering. Practically all of our patients have shown a definite degree of secondary anemia, but there has been a complete absence of pyrexia, chill, leucocytosis, throbbing, lassitude, or the usual concomitants of infectious processes.

Race

All of our cases, with one exception, have occurred in the negro. The one exception is that of a white male, in whom the lesion has likewise been atypical, simulating a phagodenic chancroidal sore with ragged ulcerated edges. His bacteriological examination was positive and he may be harboring a double infection. He, however, has not responded to treatment as in the others.

Diagnosis

We have based our clinical diagnosis entirely on the bacteriologic finding of the specific organism. This is done by making smears from the exuding surface, in which will be found numerous large mononuclear plasma cells, whose protoplasm, on proper staining, will be found studded with the characteristic encapsulated diplo-bacillus. The therapeutic result from the use of antimony intravenously, may likewise be taken as indicative of the accuracy of the diagnosis, for after three or four administrations the organism diappears entirely from the surface and cannot be found in smears.

Treatment

As pointed out by all previous writers and substantiated by the histories of cases in the Philadelphia General Hospital in years gone by, the treatment of these lesions has been most disappointing until the present, when antimony was first instituted.

Local applications of salves, escharotics, and antiseptics do no good whatsoever; vaccine therapy has been consistently a failure; excision is followed almost uniformly by recurrence before healing; arsenic is of no benefit; and X-ray alone has given us any curative results, causing a slow cicatrization, but because of the dangers associated with its use, it has been possible to apply it only once every three weeks, and therefore requiring on an average from twelve to eighteen months to establish healing. Even with X-ray the hospital experience in the years past has been disappointing, and probably at least 50 per cent of the cases had recurrences.

Some of our present cases have had two or more admissions in passing years for return of their lesions after apparent complete healing under X-ray therapy, while several have been so long inmates of the institution that they have been put on the hospital's pay-roll and work as laborers about the buildings.

Following Vianna's work, we started giving antimony intravenously in the form of tartar emetic. The initial dose of 0.04 gram was used, and this quickly advanced to a maximum dosage of 0.1 gram. Our first treatments were given daily and most

patients tolerated this until about ten doses had been given, but nearly all after that amount showed some symptoms of intolerance for the drug and we began intermitting the daily dosage, governing the time by symptomatic data. This intolerance consisted of rheumatoid pains in the joints associated with stiffness, especially seen in the early morning on rising, and most frequently located through the shoulder girdle, and as a general rule wearing off during the course of the day. There have not been in any case symptoms of an alarming character.

The drug has been prepared by dissolving 0.1 gram in 10 cc. of saline solution and is best put up and preserved by sealing, under sterile precautions in that size glass ampoules. Intravenous administration is essential.

The lesion becomes bacteriologically sterile after the second or third dose of the tartar emetic. Healing commences within forty-eight hours after the first administration, and from then on almost daily progress can be appreciated. Epithelial proliferation starts at the edges and rapidly spreads inward, while often isolated islets of epithelium in the midst of the granuloma, before not seen, or buried, start proliferation in the midst of the lesion and hurry the complete healing.

The phenomena of healing can best be pictured to you by comparing it to the use of salvarsan in somewhat similar long standing and untreated luetic skin lesions.

In some cases the administration of the drug causes a tingling, pricking sensation in the granuloma, immediately after the injection, and ofttimes an excess of mucoid secretion occurs for the first few days. Scabbing over of the surface takes place wherever the raw surfaces are in apposition, and thin crusts form around the periphery of open areas.

Results

Of our 11 personally observed cases, 8 are healed. As this is but a preliminary report we will omit history resume and tabulate them in the following table. Following the advice of Vianna we have persisted in giving all patients a course of injections after complete healing has been accomplished to prevent the possibility of recurrence.

NUMBER	NAME	SEX	ATTACK	DURATION	AREA INVOLVED	TREATMENT STARTED	CURED	DAYS	NUMBER OF DOSES	AMOUNT OF DRUG gms.	FORMER TREATMENT, REMARKS
1	Henry J.	M.	Primary	3 years	Penis, left groin, and perineum	2/11/21	3/29/21	49	23	1.85	Healed
2	Harry Q.	M.	Primary	8 months	Prepuce, left groin and perineum	2/11/21	3/26/21	46	21	1.82	Healed
3	George J.	M.	Second	6 years	Right groin and perineum	2/11/21	3/2/21	19	20	1.07	X-ray and excision, healed
4	William H.	M.	Primary	2 years	Right groin and penis	2/11/21	2/23/21	17	13	0.82	X-ray, healed
5	William P.	M.	Second	15 months	Right groin and perineum	2/12/21	2/15/21	3	3	0.23	X-ray, stopped treatment and recurred 4/15/21, healed
6	William F.	M.	Primary	2 years	Anal	2/24/21	4/2/21	37	20	1.07	Healed
7	Benj. A.	M.	Second	2 months	Penile	3/23/21					Under treatment
8	Eliz. C.	F.	Second	2½ years	Vulva, thighs	2/11/21	4/22/21	39	29	1.90	Healed
9	Marie S.	F.	Third	3 years	Vulva, left groin	1/29/21	3/29/21	31	32	1.96	Healed
10	Florence R.	F.	Primary	5 months	Vulva, perineum						Under treatment
11	Francis J. D.	M.	Primary	2 months	Left groin, perineum	4/11/21					Under treatment
12	Carey B.	M.	Third	10 years	Right groin, penis, perineum and anal						3 hospital admissions, X-ray, awaiting treatment
13	Mabel W.	F.	Primary	1 year	Vulva, perineum	3/7/21	4/18/21	42	17	1.00	Healed
14	John D.	M.	Primary	9 months	Penis						Awaiting treatment

GRANULOMA INGUINALE[1]

By ALEXANDER RANDALL, F.A.C.S., JAMES C. SMALL, M.D.,

AND

WILLIAM P. BELK, M.D., PHILADELPHIA

From the wards and laboratories of the Philadelphia General Hospital

FOLLOWING the illustrated report in May, 1920, by Symmers and Frost (18) of the finding of two cases of granuloma inguinale in Bellevue Hospital, New York, we were inclined to feel that similar cases had been seen in this vicinity, especially in the wards of the Philadelphia General Hospital.

Beginning January 1, 1921, a search was instituted with the startling result that *five* men and *two* women were found at that time in the wards suffering from granuloma inguinale in its varying forms. Clinical studies and laboratory investigations were started at once, and we wish herein to report the results of these preliminary studies carried on during the past 7 months. Subsequent admissions have raised the total number of cases to sixteen.

INCIDENCE OF THE DISEASE

There is not the slightest doubt that this supposedly tropical disease has been endemic in the vicinity of Philadelphia for the past 50 years at least. In the accurate recollections of men, both physicians and ward attendants, who have been in charge of the genito-urinary services, the condition has been recognized, though wrongly diagnosed, for the past 25 years. We have been fortunate in acquiring some photographs, made for the late Orville Horwitz, showing similar lesions that he was familiar with during his long services in the hospital, though again masquerading under a mistaken diagnosis.

It is conservative to say that 15 or more patients are admitted to this hospital yearly suffering from this disease. They receive some treatment, gain some improvement, leave the institution; and it has been the experience of those in charge that the majority return because of a recurrence of the condition within the following 2 years. The varying manifestations of the disease do not always place them in the genito-urinary wards, and patients have been observed in the dermatological, surgical, gynecological, and obstetrical wards. That the condition is endemic elsewhere in the country is practically assured. Lippincott, of Camden, has furnished us with one of our cases and has seen others since its recognition. Ross, of Richmond, has a group of cases found in Robert Bryan's clinic. Geraghty, of Baltimore, reports that he has seen the condition repeatedly in the Hopkins clinic. Walker (19) reports a case seen in San Francisco, though an importation of the disease acquired in South America. Campbell has recently reported cases from Bellevue Hospital, New York, with the citation of cases reported from other parts of the country.

HISTORY

The most complete study of the condition exists in the work of Aragao and Vianna (2), of Rio Janerio, where the disease has been present constantly and recognized for a number of years. Rio Janerio is in a southern latitude corresponding to a point between Florida and Cuba in the northern hemisphere. Within these geographical limits the condition has been met with repeatedly and hence the erroneous assumption that it is a tropical disease has prevailed. Its peculiar predilection for the negro has possibly made this assumption seem more of a fact.

The literature contains numerous scattered observations relative to the clinical aspects of small groups of cases of granuloma inguinale or the use of tartar emetic intravenously in its treatment. Cummings (7) treated a patient with antimony and potassium tartrate intramuscularly. Hoffman (10) has published a recent clinical study from Germany treating his observed cases intra-

I

venously.   Reed and Wolf (15) have en-
countered the disease in New Orleans and
have successfully treated it with antimony
intravenously.   Cuthbert (8) reports a case
from England similarly treated. Aragao (1)
in a recent article brings his bacteriological
studies up to date, claiming that though the
organism originally described by Donovan is
easily found in smears and is pathognomic,
yet it has never been cultivated.   Campbell
(4) reports three further patients observed in
Bellevue Hospital.

The use of antimony and potassium
tartrate (tartar emetic) as an intravenous
medicament, has been gaining ground rapidly.
Aragao and Vianna, in 1912, were the first to
point out its value and almost specific action
in granuloma inguinale.   Recent literature
contains numerous references to its use and
beneficial action in bilharziasis (17, 11, 14),
filariasis (12), gangosa (6), cachar sore (16),
malaria (3), leishmaniasis (5) and trypan-
osomiasis (5). The future seems brilliant
for this erstwhile popular and almost dis-
carded drug with the possibility of other
synthetic compounds.

Our first presentation of patients was on
January 24, 1921, before the Philadelphia
Urological Society, with subsequent public
expositions of the progress of the work as
follows: Philadelphia Urological Society,
March 28, 1921; American Association of
Genito-Urinary Surgeons (Richmond, Vir-
ginia) May 3, 1921, and the Philadelphia
Pathological Society, May 26, 1921. We like-
wise published a preliminary report in the
Journal of Urology June, 1921.

CHARACTER OF LESIONS

The usual history is that the lesion started
as a small papule, non-inflammatory, which
after rupture and the exudation of slightly
purulent fluid, refused to heal, and exhibited
progressive tendencies toward slow prolifera-
tion and spreading.   The typical lesion
(especially seen when involving the inguinal
region), is a flesh-red, exuberant, over-
growth of soft granulation tissue. A wire loop
for making cultures can be pushed into this
soft tissue to the depth of several millimeters.
It has absolutely no similarity to an ulcer,
with its eroding, undermining edges, and
necrotic base.   The center of the granuloma
appears slightly depressed, and there is cer-
tainly a destructive action present, but the
edges are redundant and overlap the appar-
ently healthy skin margin to the height of 6
to 8 millimeters.   Exudate is scant, mucoid
in character, of a non-offensive odor, and when
wiped with gauze is easily removed, leaving a
clean, red, bleeding surface, similar in every
respect to a large area of healthy granulation
tissue as seen in clean surgical wounds.
This picture varies according to the duration
size, and location.   The older lesions show at
times tendencies toward cicatrization at some
points, while spreading in others, but this
occurs only when flat, non-chafing surfaces
are involved.   Large lesions, especially those
of the perineum, become bulbous, simulating
condylomata acuminata, with large rounded
heads of new-growth, the heads ofttimes with
pearly white surfaces of epithelization, and
deep crypts with raw granulomatous surfaces.
Secondary infection here causes the clean,
odorless character to change.

As indicated by the name, the most fre-
quent location is in the groin spreading
upward as far as the anterior superior spine
and downward through the fold of the
groin, frequently involving the perineum, and
in some cases following the fold of the nates
and spreading to the buttocks.   Prepucial
lesions are likewise frequently associated and
at times primary, and involvement here has
given us the most destructive picture with a
gradual erosion of the glans and even the shaft
of the penis.   In the male we have had 4
cases where the lesion was limited to the
groin alone: 2 cases of penile involvement;
1 limited to the anal region alone; and the
remainder with multiple involvement includ-
ing the perineum.

In the female the labia majora suffer most,
though groin lesions are again characteristic;
and once the external genitalia become in-
volved, the entire vulvoperineal region
suffers and the spread is the same as in the
male.   We have observed extension in two
cases into the vagina and rectum.   The labia
swell enormously and become almost
elephantine.

In certain patients the history apparently points to a granuloma infection superimposed upon a prior existent genital lesion.

SYMPTOMS

The patient has few subjective symptoms. They suffer no pain or discomfort unless the involved areas are so placed as to cause chafing. The granuloma is practically painless to the touch, and only deep pinching up of the mass will cause suffering. Practically all of our patients have shown a marked degree of secondary anæmia, but there has been a complete absence of pyrexia, chill, leucocytosis, throbbing, lassitude, or the usual concomitants of infectious processes. Their blood counts show a decrease in red cells commeasurate to their anæmia. No leucocytosis, eosinophilia or other characteristic change has been observed in the white blood cells. Fragility tests and blood-platelet counts are likewise normal.

Wassermann tests have been negative with a few exceptions where undoubtedly a double infection has been present, and in these energetic antiluetic treatment has been devoid of effect upon the granuloma, and no other evidence of lues has been present (where the Wassermann test was positive) except a history of prior infection.

RACE

All of our cases, with one exception, have occurred in the negro. The one exception is that of a white male, in whom the lesion has likewise been atypical, simulating a phagodenic chancroidal sore with ragged ulcerated edges. His bacteriological examination was positive and he may be harboring a double infection. He, however, has responded to treatment slowly, and healing has progressed under specific treatment with antimony, after being entirely rebellious to arsenic and all local applications, though it must be recorded that complete and permanent cure has not been obtained in his case to date.

DIAGNOSIS

We have based our diagnosis on the fairly characteristic clinical pictures, and also especially on the bacteriological findings of the specific organism. This latter is done by making smears from the exuding surface, in which will be found numerous large mononuclear plasma cells the protoplasm of which, on proper staining, will be found studded with the characteristic encapsulated bacillus originally described by Donovan. The therapeutic result from the use of antimony intravenously may likewise be taken as indicative of the accuracy of the diagnosis, for, after three or four administrations, the organism disappears entirely from the surface and cannot be found in the smears, and healing promptly follows.

That the condition has been constantly present in the hospital wards of this vicinity carries with it the necessity that it has masqueraded under other and faulty diagnoses. Many have been considered chancroidal sores to which it bears no relation (except where secondarily infected as in the perineal lesions), for the ulcerated, undermined edges and the foul purulent discharge are absent. Tertiary syphilis with its varying manifestations has claimed others, especially before the days of the Wassermann test and arsenic therapy. Condylomata acuminata, especially when seen in the female, may have been confusing, while condylomata lata bear close resemblance to the lesion of granuloma when the latter occur about the anus (see Case 6).

In our genito-urinary wards, the diagnosis has been for the past two decades tuberculosis cutis, and this I find was what the late Orville Horwitz considered it. A. A. Uhle, shortly before his death, was interested in the etiology of these cases, and in conjunction with Randle Rosenberger undertook some investigations in an attempt to establish the tuberculous nature of the lesion but, failing to demonstrate to their satisfaction that this infection was present, carried the work no further. Its similarity to lupus and the improvement under X-ray therapy was always held as the sole argument in favor of this diagnosis.

Any pudendal sore, resistant to the ordinary surgical antiseptics, unimproved by arsenical therapy, of long duration, and especially when devoid of pain, should be searched
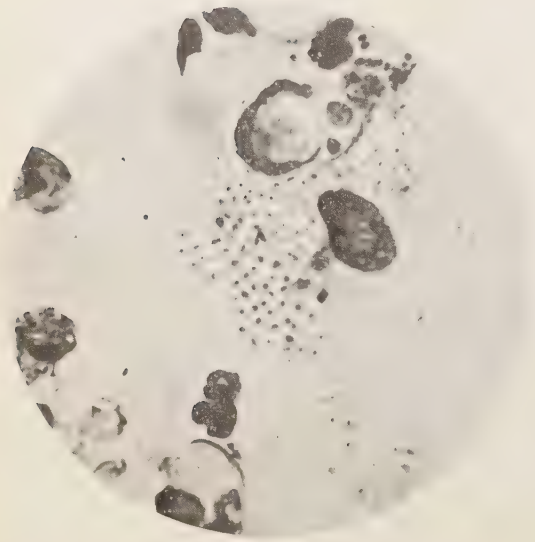
Fig. 1. Smear from lesion. Wright's stain. x, 800. Donovan's organisms in and about mononuclear cells. A rounded "nest" of non-encapsulated organisms appears in the disintegrating cytoplasm of one of the cells.

Fig. 2. Smear from lesion; Wright's stain. x, 1200. Intact mononuclear cell showing cytoplasm studded with Donovan's organisms—capsules narrow or absent.

for the specific organism of granuloma inguinale and given the advantage of antimonial treatment.

BACTERIOLOGICAL METHODS AND DIAGNOSIS

Direct smears from the lesions, properly prepared and stained, constitute a very reliable method of diagnosis. The material is best collected by means of a stiff inoculating wire loop which can be inserted quite deeply into the friable granulations of the lesions, rotated gently and withdrawn quickly in order to bring an inoculum from the deeper parts. Surface contamination can be minimized by first sponging off any surface exudate with sterile gauze. Suitable material for diagnostic smears may be obtained also on small cotton swabs from such a cleansed surface of the lesion, but where cultures are to be attempted material from the deeper parts of the lesion is to be desired. Thin spreads of this material are essential. These are dried quickly in air and stained either by the Wright's or the Giemsa method. Wright's staining is the more rapid and has given satisfactory results. The proper differentiation of the stained smear in distilled water is the chief technical difficulty. Even with the most intense staining this differentiation should not be carried out

for more than 15 or 20 seconds. Overdifferentiation completely decolorizes the capsules of the organisms; while underdifferentiation fails to bring out detail and contrast between the body proper and the capsule.

The best staining results show the organisms as small, rounded, pink bodies with a dark blue coccoid body in the center; or, more frequently as oval pink bodies with a blue bacillary or diplococcoid body occupying the longitudinal axis. The pink outer zone is a wide capsule. The dark blue central bodies represent metachromatic granules within the body proper. The true outline of the body proper can be studied only after the capsule has been entirely decolorized.

In stained preparations from the lesions, some areas will show organisms with the capsules stained a pale blue and with obscurely differentiated central bodies; other areas will show well-defined dark blue metachromatic granules surrounded by a pink capsule; and still other areas where the capsules have been entirely destained and in which the organisms appear as short, thick bacilli with blunt, rounded ends occupied by the dark blue metachromatic granules, presenting a true bipolar stained appearance with the intervening body shaft stained a pale

Fig. 3. Preparation from acid dextrose agar culture; Wright's stain. x, 1200. Capsules stained, typical morphology.

Fig. 4. Young broth culture; Wright's stain. x, 800. Bipolar staining and solid staining of organisms. No capsules.

blue. Always a few organisms, usually shorter than those just described, are seen to stain solidly a deep blue.

The organisms are found within the cytoplasm of large mononuclear cells. In such they either have well-defined capsules, or appear in nests occupying a rounded area within the cell and revealing no capsules. Within these nests the bipolar staining may at times be observed. The polymorphonuclear leucocytes do not contain encapsulated forms. Encapsulated organisms may appear free, or in relation to cellular detritus, chiefly in groups and in the neighborhood of large naked nuclei of disintegrating mononuclear cells.

Smears from the lesions are remarkably sparse in other bacteria as compared with smear preparations from the other types of ulcerative lesions about the genitalia. Staphylococci, streptococci, diphtheroid bacilli, and bacilli of the morphology and staining characters of the colon group may be observed widely scattered, or grouped within the polymorphonuclear leucocytes.

Cultures from the lesions. Material collected from the lesions has been inoculated on various types of media and grown under different conditions. In the cases of three patients an organism has been obtained, which,

in stained preparations from the cultures, resembles the organisms seen in the mononuclear cells in stained preparations of the exudate directly from the lesions. Failure to obtain this organism in cultures from all the lesions as well as subsequent failure to produce chronic lesions in animals by inoculation of the organisms, has led us to study carefully the different bacteria growing in cultures from the lesions. The general plan of this study will be mentioned later.

Aragao and Vianna (2) called attention to an organism grown in three of seven granuloma lesions studied, and described it under the name of calymmatobacterium granulomatis. Their description of this organism places it within the group of gram-negative encapsulated bacilli and does not differentiate it from the bacillus mucosus capsulatus group sufficiently to warrant its separate classification and new nomenclature. They presented this organism as the specific causative agent of granuloma inguinale on rather incomplete evidence. Since then one of them (Aragao, 1) has reported further studies with the conclusion that the organism described by them in cultures is not the causative agent of the disease, stating further that the specific organism has not been cultured. Walker (19)

in one case isolated a gram-negative, en-
capsulated bacillus. He was unable to pro-
duce chronic granulomatous lesions in animals,
nor in several instances in men. Lynch (13)
has grown an organism in his cases but does
not describe it.

In our study, plate cultures have been
made on acid dextrose agar (Ph. 6.6) and
infusion blood agar (Ph. 7.4) by surface
inoculation and incubated at 37° C. Material
from the lesions has also been inoculated
heavily into tubes containing about 5 cubic
centimeters of peptone water. From such
tubes after several hours' incubation at 37° C.,
anaerobic and partial oxygen tension cultures
have been made. Plate cultures on Sabour-
auds medium have been carried at 20° C. for
long incubation periods and studied for molds
and yeasts.

In all cultures search was made first for
organisms which, when stained with Wright's
stain, might present any of the distinctive
staining and morphologic characters of the
organisms uniformly found in the direct
smear preparations from the lesions. This
required the isolation of organisms in pure
culture and growth in many subcultures in
order that the morphology and staining
properties might be observed for the growths
of the particular organism on various kinds
of media. Where an organism of the encap-
sulated, gram-negative bacillus group was
isolated, the strain was preserved to be sub-
jected to detailed bacteriological study. The
finding of such a strain did not modify the
more tedious study of the morphology and
staining properties of the other organisms
appearing in the primary cultures from any
particular patient. The protean-staining re-
sults with a Romanowsky stain are soon very
well appreciated when it is employed in such
a study of bacteria. Repeated stained prep-
arations of an organism are frequently
necessary in order to exclude these aberrant
results which may present appearances sug-
gestive of the metachromatic staining con-
stantly observed in the Donovan organisms
of the direct smears from granuloma lesions.
The organisms found to present these staining
characters, with any degree of consistency,
were next subjected to tests planned to

demonstrate the effect of tartar emetic upon
their growth in suitable media in the test
tube. If any appreciable inhibitory effect
was noted, animals were inoculated intra-
peritoneally, cutaneously, and subcutane-
ously. The general plan of this animal
experimental work was first to inoculate
large doses of the culture intraperitoneally
into white mice. At 2, 4, and 6 hours after
inoculation, stained preparations of the peri-
toneal exudate were made to determine, first,
the character of the cellular reaction (whether
mononuclear or polymorphonuclear); second,
the type of cell phagocytosing the bacteria
injected; third, to study the morphology and
staining of the bacteria as they occurred free
in the exudate or included in the cells; and
fourth, to gain some idea of the pathogenicity
of the organism for white mice. In some
instances guinea pigs were used also in the
same manner as the mice.

Animals inoculated cutaneously and sub-
cutaneously were observed over long periods
for the development of lesions, which latter
appearing were studied from time to time by
means of stained smears and by cultures.

By employing the above methods in the
cases of 12 patients, in all of whom the
Donovan organisms were found in the direct
smears from the lesions, we have obtained an
organism in culture closely resembling these
bodies in three instances. These organisms
have proved to be encapsulated bacilli of the
bacillus mucosus capsulatus group, and very
probably correspond to the organisms re-
ported by other workers in cultures from simi-
lar lesions. They grow freely on all the ordi-
nary culture media and their growth is favored
by an acid reaction. The acidity of the media
may be increased to a point where the growth
of the ordinary contaminating bacteria is
markedly inhibited before any appreciable
inhibition of the growth of this organism is
observed. This is especially true if a simple
carbohydrate is added to the media.

The surface growth of these organisms is
quite characteristically that of the Fried-
laender bacillus. The colonies appear as
slightly gray-white, translucent, glistening,
dome-shaped elevations on round regular
bases from 1 to 3 millimeters in diameter.

When touched with an inoculating wire they appear quite viscid, having the appearance and consistency of thin starch paste. By transmitted light they are translucent and have a slightly brownish tinge. They are usually the largest colonies appearing in the mixed primary cultures and are very readily recognized. In subcultures the growth is profuse on all the simpler laboratory media and the growth on agar, gelatin, or coagulated blood serum does not differ essentially from that described above. In fluid media diffuse turbidity develops with a surface ring of growth tending to adhere to the sides of the tube and to climb slightly above the level of the liquid. Later sedimentation occurs. Growth is profuse even in 1 per cent peptone water. In litmus milk, there is acid formation and coagulation within 24 hours. On potato growth is abundant, moist and brown, with decided blackening of the potato.

In stained smears preferably from the acid glucose agar cultures, wide capsules are easily demonstrated, so that the organisms appear as do the Donovan organisms in the exudate from the lesions. In the stained smears from broth cultures, the capsules are not demonstrated, the organisms appearing as short, plump bacilli, exhibiting irregular staining, for the most part showing a dark area at either pole, with a pale, intervening area. In old cultures, especially in a medium containing a carbohydrate which has fermented with decided acid production, long forms are found. These forms also stain irregularly, presenting dark blue, banded areas, alternating with pale areas throughout the length of the organism.

The organism is a gram negative, non-motile, non-sporulent, encapsulated bacillus, which shows metachromatic granules as well as capsules with Romanowsky staining. It does not liquefy gelatin or coagulate serum. Freshly isolated cultures hæmolize blood. Milk is coagulated and acidified. Indol is not produced. The organism ferments dextrose, lévulose, lactose, galactose, saccharose, maltose, mannit, arabinose, salicin, inulin, and dextrin. It does not ferment dulcit nor rice starch.

Repeated cultures have failed to yield this organism in the other patients, so that a thorough search of the bacteria growing in all the primary cultures was conducted to determine whether among the colonies growing there might be organisms showing other gross cultural characters, but which might upon proper staining show some of the characteristics of the Donovan bodies. Many strains of different bacteria have been isolated because of some suggestive staining property with the Wright's stain and a number of these have been carried through to animal inoculation for the purpose of studying the appearance of the particular organism in the animal exudates. In no instance was found an organism which tended to occur in the mononuclear cells, although in many such exudates when examined within 6 hours after inoculation there appeared considerable numbers of mononuclear cells. The morphology of Donovan organisms was not approximated by any of the organisms examined in these exudates, except by the three strains of encapsulated bacilli as mentioned above.

Animal inoculations. The three strains of encapsulated bacilli isolated from granuloma lesions have been studied in detail by experiments in which six strains of the bacillus mucosus capsulatus group (Friedlaender's) isolated from the throats, sputum, and empyema fluid of patients in this hospital have been carried in parallel experiments. These experiments will be reported in a subsequent paper; we simply say at this time that these studies have failed to show any distinctive properties which might serve to differentiate the strains of granuloma origin from those of respiratory origin. Lesions produced in experimental animals with strains of granuloma origin may just as easily be produced with strains of respiratory origin and in our experience the lesions appear identical.

Experiments with strains of granuloma origin. Intraperitoneal inoculations of mice and guinea pigs have proved rapidly fatal. The exudate when examined early, 2, 4, and 6 hours after inoculation, shows a mononuclear cell reaction; later the polymorphonuclear cells predominate. The bacteria occur for the most part free in the fluid and present wide capsules. They resemble the Donovan bodies with well-developed capsules. Some

when superimposed on the mononuclear cells are very characteristic, but the rounded nests of bacteria, showing only narrow capsules or no capsules, lying unmistakenly within the mononuclear cell cytoplasm, have in no instances been observed.

Cutaneous inoculations of mice, guinea pigs, rabbits, cats, and dogs have invariably failed to produce lesions. Abraded skin areas over the arm of an adult colored male (Case 12) were inoculated, (a) with granuloma strain I; (b) with granuloma strain II; (c) with a strain of Friedlaender's bacillus of mouth origin; and (d) with sterile normal salt solution. These were observed for a period of 19 days before the treatment with tartar emetic was started. All crusted over and healed promptly.[1]

Subcutaneous inoculations of guinea pigs, cats, and dogs have failed to produce lesions. Subcutaneous inoculations of mice have at times resulted in the death of the animal from a generalized infection; at other times in abscess formation which healed promptly either with or without breaking down with ulcer formation.

Subcutaneous inoculations of rabbits with 1 cubic centimeter of broth culture of the organisms have produced focal lesions. Beginning as firm, indurated masses, they appeared after 7 to 10 days as large doughy abscesses. These might point in one or more places, breaking down to form well-defined ulcers in the depths of which appeared the tough, cheesy, necrotic material which we have come to regard as the typical contents of abscesses produced experimentally in rabbits by the Friedlaender bacillus. These abscesses drained imperfectly through the spontaneous openings. Firm pressure on the abscess adjacent to the ulcer expressed the necrotic material and tended to produce some bleeding from the margin as well as from the depths of the ulcer. Evacuation of this material hastened healing. Left to themselves these lesions would heal slowly, the necrotic material being in part thrown off and in part absorbed. The lesions always healed spontaneously in from 3 to 7 weeks after inoculation. In the necrotic material and from the granulations bordering the ulcer, the encap-

sulated bacilli could be demonstrated by smear and culture. In the smear preparations from the granulating border, the nests of bacteria within mononuclear cells could not be demonstrated. In some cases the typical doughy abscess would not rupture, healing taking place after absorption of the necrotic material.

In mice and rabbits, some experiments were planned with the view of attempting to establish symbolic relations in an experimental lesion between the encapsulated bacilli of granuloma origin and some of the other types of bacteria isolated from granuloma lesions. Bacteria of the staphylococcus, colon, and diphtheroid group were used, being injected simultaneously with the inoculum of the encapsulated bacillus. The lesions produced by the encapsulated bacilli following subcutaneous injection were not modified by this method of inoculation, except in rabbits when injected with staphylococcus aureus, with which abscess formed more promptly and always ruptured spontaneously. The rate of healing did not appear to be affected.

HISTOPATHOLOGY

Stained sections of granuloma inguinale show a superficial cellular area surmounted on a base of dense, hyaline, connective tissue. The transition is rather sudden, but no distinct line of demarcation separates the two elements. The cellular area is composed of a young connective tissue, relatively small in amount, many endothelial leucocytes, and a smaller number of polymorphonuclear neutrophiles. The proportion of the latter varies considerably, appearing most numerous in untreated cases. They are probably an index of secondary infection. Many lymphocytes are also present, and an occasional eosinophile. Blood-vessel formation is present as in any active granulation tissue. At the margin of the granulation, the squamous epithelium of the skin is seen partially destroyed and replaced. Further out this merges into normal skin, under which, however, the subcutaneous tissues are infiltrated for a little distance by round cells. This would indicate that the lesions extend somewhat farther than would appear on superficial inspection of the granulating area.

[1] Recently, in 2 patients, similar inoculations have yielded negative results.

A feature worthy of note is the proliferation of squamous epithelium near the edges of the granuloma, where finger-like projections extend for some distance into the deeper tissues. In some cases this suggested a squamous-cell carcinoma.

After treatment for some time with antimony injections, the dense fibrous tissue is seen to have replaced the granulations to a large extent. Small collections of lymphocytes remain in this fibrous growth, and a smaller number of endothelial cells. Polymorphonuclear cells have entirely disappeared. A bipolar bacillus, without capsule, has been stained (by Giemsa's stain) in tissues, and these have been found only in the large mononuclear cells. The encapsulated organisms described have not been stained in tissues in this laboratory. However, smears made from the tissues immediately prior to fixation, or at the bedside during biopsy, and stained with Wright's stain, showed them in many cases.

Individual pathological studies appear with their case histories. Sections from one of the experimental animals (Rabbit 3) gave the following: Pieces of tissue from the subcutaneous mass in abdominal wall were fixed in 4 per cent formalin in normal sodium chloride and in Schaudin's fixative. The first were stained with hæmatoxylin and eosin, the last with Giemsa's stain. On examination, the following features were noted: a sparse growth of young connective tissue supported a very cellular mass, the cells were endothelioid and polymorphonuclear neutrophiles in about equal numbers; many small lymphocytes and an occasional eosinophile. New blood vessels were rather numerous, and considerable blood was present. Many small areas of necrosis were scattered throughout. In sections stained with Giemsa's stain a few coccoid bodies without capsules were seen in some mononuclear cells, but not in other phagocytes. The picture was strikingly similar to that of untreated granuloma lesions in man, except for the necrotic areas.

PROGNOSIS

As pointed out by all previous writers and substantiated by the histories of cases in the Philadelphia General Hospital in years gone by, the treatment of these lesions has been most disappointing until the present when antimony therapy was first instituted.

Local applications of salves, escharotics, and antiseptics do no good whatsoever; vaccine therapy has failed consistently; excision is followed almost uniformly by recurrence before healing; arsenic is of no benefit; and X-ray alone has been somewhat beneficial, causing a slow cicatrization, but because of the dangers associated with its use, it has been possible to apply it only once every 3 weeks, and therefore requiring on an average from 12 to 18 months to establish healing. Even with X-ray the hospital experience in the years past has been disappointing and probably at least 50 per cent of the cases returned with recurrences.

Some of our present cases have had two or more admissions in passing years for return of their lesions after apparent complete healing under X-ray therapy, while several have been inmates of the institution for so long that they have been put on the hospital's pay-roll and work as laborers about the buildings. That the condition has been in the experience of this hospital the actual cause of the death of the individual can be recalled by some of the older ward attendants, though not experienced in recent years since X-ray therapy has been used. Our personal experience is limited to the amount of destruction seen in Case 16, where the disease is known to have existed 10 years, causing a complete erosion of the penis.

With the proper application of the new antimony therapy the prognosis becomes extremely good, for the brilliant results seen and herein recorded place this drug as one of the small group of actual specific remedial agents and rapid and apparently complete cures can now be expected.

RESULTS

Of our 16 cases, we have accomplished a rapid and apparently complete cure in 15. The one exception is the case of a white male, before mentioned, whose lesion was not typical, whose organisms were not entirely characteristic, but who was given the advantage of the treatment when all other administrations had failed over a period of 7 months.

He has shown definite improvement (nowhere near as rapid as the true cases), but not yet complete healing (Case 14). We have had two recurrences (Cases 6 and 9), both due to early neglect of treatment and both rapidly healed on re-administration of tartar emetic. We have not seen in a single case any alarming symptoms from the use of the drug, and though the abbreviated case reports do not allow of the exposition of the complete case study, suffice it to say, that no blood or urine changes have been noted as evidence of its toxic effect or to contra-indicate its extensive use as a therapeutic agent. The brilliant recoveries that these patients have made from conditions of years' duration and manifold other forms of therapy, have been as inspiring to their attending physicians as they have been satisfactory to the patients themselves, who have appreciated more than any one else their first permanent relief from an apparently incurable condition. Several (Cases 2, 4, and 5) who were markedly anæmic and emaciated, have shown a general systematic inprovement with increase in hæmoglobin and decided increase in body weight.

TREATMENT

Following Vianna's work, we started giving antimony intravenously in the form of tartar emetic. The initial dose of 0.04 gram was used, and this quickly advanced to a maximum dosage of 0.10 gram. Our first treatments were given daily and most patients tolerated this until about ten doses had been given, but nearly all after that amount showed some symptoms of intolerance for the drug. We then began intermitting the daily dosage, governing the time by symptomatic data. This intolerance consisted of rheumatoid pains in the joints associated with stiffness, especially seen in the early morning on rising, most frequently located through the shoulder girdle, and as a rule wearing off during the course of the day. There have not been in any case symptoms of an alarming character.

The drug has been prepared by dissolving 0.1 gram in 10 cubic centimeters of sterile normal saline solution and is best preserved in sealed sterile ampules. Intravenous administration is essential.

The typical encapsulated organisms cannot be demonstrated in smears from the lesion after the second or third dose of the tartar emetic. Healing commences within 48 hours after the first administration, and from then on almost daily progress can be appreciated. Epithelial proliferation starts at the edges and rapidly spreads inward, while often isolated islets of epithelium in the midst of the granuloma, before not seen, or buried, start proliferation in the midst of the lesion and hurry the complete healing.

The phenomena of healing can best be pictured by comparing it to the use of salvarsan in somewhat similar long standing and untreated luetic skin lesions.

In some cases the administration of the drug causes a tingling, pricking sensation in the granuloma, immediately after the injection and ofttimes an excess of mucoid secretion occurs for the first few days. Scabbing over of the surface takes place whenever the raw surfaces are in apposition, and thin crusts form around the periphery of open areas.

The amount of drug administration necessary to complete a cure appears to be commeasurate with the extent of the lesion and the amount of epithelization necessary. Penile and groin lesions heal rapidly, while vulval and perineal, apparently on account of the apposition of surfaces, respond more slowly and show a tendency to dry and scab over first thus causing slower healing.

Through the courtesy of Professor John J. Abel, of the pharmacological department, Johns Hopkins Medical School, we had placed in our hands two synthetic antimony compounds for trial. One of these (sodium antimony thioglycollate), it will be noted, was used in Case 12, with brilliant results, and a further report will be made later.

Our simplest case required but four doses for complete epithelization of an area the size of a silver quarter: this patient then neglected treatment and had a recurrence 6 weeks later. The highest dosage for healing was in one of the females who had 1.96 grams of the drug in 32 injections. Following the advice of Vianna, we have advised all our patients to persist in taking weekly injections after com-

plete healing for at least 12 doses and in none adhering to this procedure have we observed a recurrence.

We wish, in closing to express our gratitude to three of the resident staff of the Philadelphia General Hospital; Drs. R. Bradley, P. P. Bailey and P. E. Lueke, for their personal interest and keen attention, which combined with technical ability of high degree in handling the intravenous medication made these results possible.

CONCLUSIONS

1. Granuloma inguinale, long considered a tropical disease, is endemic in the temperate zone of the United States.

2. Its diagnosis is dependent on (1) the characteristic local lesion, (2) the marked predominance in the negro race, (3) and the finding of the specific organism originally described by Donovan.

3. These organisms we have demonstrated in smears from granuloma lesions in 12 patients in our series of 16. In the other 4 instances laboratory examinations were not made.

4. An encapsulated bacillus, which when stained from cultures, resembles this organism, has been isolated from 3 of the 12 patients studied culturally. This bacillus is a member of the bacillus mucous capsulatus group.

5. The question remains as to whether the organism seen in smears and that obtained in cultures, which appear so similar, are identical.

6. Abscesses with spontaneous rupture and ulcer formation have been produced in rabbits by subcutaneous inoculation. These heal spontaneously in from 3 to 7 weeks and grossly cannot be regarded as granulomata although the walls of these abscesses on histological examination present granulation tissue not to be differentiated from that of the granuloma lesions. Friedlaender's bacillus forms similar lesions.

7. A few experiments attempting to establish symbiotic relationships between the encapsulated bacilli from granuloma lesions and staphylococci, colon bacilli, and diphtheroids in experimental lesions have failed. More work of this nature should be undertaken.

8. Treatment with tartar emetic intravenously acts as a specific, and rapid healing may be expected with the prompt disappearance of the specific organism.

9. We have experienced no contra-indication to the intravenous use of this drug up to doses as high as 0.1 gram.

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CASE REPORTS[1]

CASE 1. H. Q., male, negro, age 39, admitted January 3, 1921, complaining of ulceration of left groin, foreskin, and perineum. Patient born in the county bordering Philadelphia, and has spent all of his life hereabouts. He has never been out of the United States, never south of Baltimore nor north of New York City. He had gonorrhœa last spring, preceding the present trouble by 4 or 5 weeks. The condition began about 8 months ago as a small pimple in the left groin; it was only the size of a pin's head and not at all painful. It rapidly grew to the size of a quarter of a dollar, then broke down, discharging a purulent content, and has remained an open lesion ever since. Soon after the appearance of the lesion in the groin, and before the pimple in the groin broke down a similar one developed on the foreskin. This likewise became an open sore and the two have continually increased in size to the present condition. Examination reveals an area two finger breadths broad, extending from the inferior iliac spine down through the inguinal fold onto the perineum, is the seat of a raw, flesh-red, soft, and oozing granulomatous mass. It is not depressed and ulcerated, but actually raised above the level of the surrounding skin. Similar lesions occur on the left side of the scrotum and encircling the margin of the foreskin preventing its retraction. The

[1] First three case reports in semi-detail to show typical histories, types of reaction, mode of administration and promptness of healing. Remaining histories extensively abbreviated on account of space.

center of the large groin sore is depressed, though uniformly covered with the soft, papillomatous proliferations. There is no offensive discharge, but a sanguinous exudate: no pain, except on deep pinching: and no enlargement of the underlying lymph glands.

Laboratory notes. January 25, 1921. Smears, Gram stain, staphylococci, diplococci and diphtheroids. Fontana's stain, few loosely coiled spirochætæ. Geimsa's stain, red blood cells, polymorphonuclears and large mononuclear cells, no granuloma bodies. Cultures, staphylococci, bacillus coli, and diphtheroids. February 1, 1921, smears (Wright's stain) positive for granuloma bodies. Culture on Sabouraud's medium, no growth after 72 hours. February 12, 1921, blood count, hæmoglobin, 45 per cent, red blood cells 1,000,000; white blood cells, 10,700; polymorphonuclear, 60 per cent; lymphocytes, 36 per cent; mononuclears, 2 per cent; eosinophiles, 2 per cent. February 19, 1921, blood count, hæmoglobin, 59 per cent, red blood cells, 3,380,000; white blood cells, 10,150; polymorphonuclear, 55 per cent; lymphocytes, 44 per cent; eosinophiles, 1 per cent. March 28, 1921, fragility test, complete hæmolysis, 0.20. Complete inhibition, 0.44. March 31, 1921, blood platelet count, 460,000. Reticulated reds, 0.52 per cent. April 4, 1921, smears (Wright's) no granuloma bodies. (Treatment started February 11, 1921.) Staphylococci, diphtheroids. Cultures—staphylococci, diphtheroids. NOTE—Cultures at no time from this patient were positive for the Friedlaender-like bacillus.

Histopathology. Section taken from margin of lesion. Fixed in 4 per cent formalin in normal saline and in Schaudin's solution. Stained with hæmatoxylin and eosin, and Giemsa. Showed typical picture as described above. Smear made at bedside, stained by Giemsa, showed encapsulated diplococci forms, intra- and extracellular. Section from prepuce, obtained at circumcision on May 9, 1921, after tartar emetic treatment, shows a small ulcer, pinhead size. Stained as above. Marked fibrosis; minute area containing many lymphocytes, a few endothelial cells, occasional polymorphonuclear cells. The squamous epithelium of the skin appeared practically normal.

Treatment. February 11, 1921, 0.05 gram tartar emetic given intravenously. Fifteen minutes after the injection, patient had a slight chill followed by headache. Urine analysis of today negative throughout. February 12, 1921, 0.05 gram tartar emetic given intravenously. Slept well last night and experienced nothing further than above mentioned chill. Today normal. February 13, 1921, surface of granuloma not so moist as formally, and of a lighter hue with less bleeding. Edges seem somewhat retracted and flattened. No local sensation experienced with the injections. Given 0.05 gram intravenously. February 15, 1921, wound and patient not disturbed yesterday. Dressing today is quite moist with a serous discharge. Edges show marked retraction, and epithelium is apparently spreading inward. Granulations less exuberant. 0.05 gram tartar emetic intravenously. No reaction. February 17, 1921, there is without doubt a decrease in the amount of serum which exudes from the granulations during the past 24 hours. Three little islands of epithelium have made their appearance near the center of the groin lesion. The epithelium from the edges is growing inward. The lesion on the prepuce is definitely smaller, and the amount of induration is decreased, allowing further retraction of the prepuce. 0.08 gram tartar emetic intravenously. No reaction. February 18, 1921, color of granulations is changing from beefy-red to salmon color. Decrease in size of lesion continues. 0.08 gram tartar emetic intravenously. No reaction. February 21, 1921, 0.08 gram tartar emetic intravenously. No reaction. February 22, 1921, 0.10 gram tartar emetic

intravenously. No reaction. February 23, 1921, 0.10 gram tartar emetic intravenously. No reaction. February 24, 1921, 0.10 gram tartar emetic intravenously. No reaction. Epithelium has continued to proliferate actively. The islands in the center of the groin lesion now measure ½ by 8 centimeters. No systematic effect noted from injections. Dosage of 0.10 gram given on following dates, March 2, 3, 4, 7, 8, 9, 16, 19, 23, 26, 29, 31, April 11, 15, 19, 26, May 4, 14, 23. May 9, 1921, lesion so far healed that patient was prepared for circumcision and same successfully performed.

CASE 2. M. S., female, negro, age 21, admitted November, 1920, complaining of genital sores. Born and lived in Philadelphia, married, has had three full term pregnancies. Since initial sexual act in 1914, has had yellowish vaginal discharge and 1 month following this the right labium majorum enlarged, and within 1 week, it had become such a size as to cover the opposite labium. It was not painful, nor was there any visible excoriation, abrasion, ulceration, or bleeding. This condition persisted for 1 month, then disappeared in 2 weeks time without any treatment. In December, 1917, she experienced a stinging sensation again in the right labium and found a small "pimple-like" sore there which she broke. Following this several similar sores formed, rather slowly, and coalesced. There was no soreness with these lesions until after 3 months, at which time patient was admitted to the Philadelphia General Hospital (February 13, 1918) because of condition of vulva and 8 months' pregnancy. On examination, pudendal lesions and a left bubo considered syphilitic, Wassermann reported 4+. She was given five doses of arsenobenzol and discharged from hospital, June 20, 1918, having been delivered of a living child, the bubo healed and vulva nearly healed. Patient describes this first lesion as being red, lumpy, bleeding easily, growing rather rapidly and raised off the surface of the skin. During the summer of 1918, she attended the dispensary regularly for antisyphilitic treatment. July 11, 1919, she was readmitted to the hospital. The following notes have been extracted from her history. Complaint, sores on privates which began to break out as soon as she left hospital last year; they have steadily grown worse to date. General appearance is emaciated. Labia are swollen and ulcerated at anus, inguinal lymph glands are markedly swollen. Purulent discharge from vagina. September 11, 1919, labia majora were much swollen; right labium has tumor mass on it, which is hard, firm, not tender. Lower third is denuded of epithelium, on cleansing shows surface ulcerated and granulating. Left labium less swollen than the right, has a soft tumor, tender on pressure: lower fourth ulcerated and granulating. Urethral orifice surrounded by soft, tender, finger-like processes. Inguinal glands much enlarged; ulcerated on left side and nearly healed. Gland on right side open and ulcerating. December 14, 1919, the condition has been pronounced tuberculosis cutis by genital-urinary chief, and syphilis by the skin chief. Patient has had marked antisyphilitic treatment with no improvement. *Laboratory report.* Histological reports: tissue resembles, or is, epithelioma. Bacteriological reports: no tubercle bacilli found in smears. Blood Wassermann, July 12, 1919, 4+. September 18, 1919, negative. October 27, 1919, negative. January 31, 1920, 1+. Constant irregular fever with slight increases in pulse and respiration of irregular character. Fever seldom at or above 101°. Treatment has been practically antisyphilitic all the way through, although five X-ray applications were made, evidently with lupus vulvæ in mind. Patient was discharged in January 1920.

At time of third admission in November, 1920, the patient was in a weakened and emaciated state, her

appetite a capricious affair, she was fretful and nervous, found it difficult to sleep, and had to be moved with extreme care, because of the pain in a very much hypertrophied vulva, the surface of which was granular, nodular, with a tendency to bleed at the slightest provocation. The diagnosis of tuberculosis of the vulva made on her previous admissions was adhered to once more, and confirmed by chief of service. X-ray treatments were instituted at once; she was sent to the X-ray department every 3 weeks, and by the middle of January, 1920, there was evidence of improvement, noted more especially in regard to her general condition, than in the appearance of the local lesion, in fact it was noted on her chart that the granular process on the vulva was becoming more extensive. A section taken in December, 1920, for histological examination was reported as follows: "Tissue shows considerable proliferation of the squamous cell layer, which extends rather deeply into the underlying tissue. No pearls are present; otherwise the section shows a diffuse infiltration by polymorphonuclear cells and there is considerable free hæmorrhage. Diagnosis: chronic inflammatory tissue; suggests lupus. Stain for tubercle bacilli is negative." The latter part of January, 1921, a tentative diagnosis of granuloma inguinale was made, and confirmed by laboratory methods (smears and section). The patient's condition at the time the intravenous injections of the tartrate of antimony and potassium were started, was very poor; she was extremely emaciated, weighing but 87 pounds, the pale color of all of her mucous membranes favored a rather severe secondary anæmia, and, as stated before, she had a rather poor appetite, was irritable and easily hurt when moved. The lesion locally, as follows: *Left inguinale region:* an area 2 centimeters above the Poupart's ligament and parallel with it; measured 7 centimeters in length and varies from 0.5 to 1.5 centimeters in width. The border is irregular in outline, but very definitely raised off the surface of the skin; the color is a vivid red, with small bleeding areas here and there, where the surface has been abraded slightly by the removal of bandage. The surface has a nodular appearance, is slightly moist; there is no evidence of ulceration, the whole affair is a marked piling up and proliferation of granulation tissue. There is a peculiarly offensive odor when the lesion is exposed. No enlargement of the inguinal glands noted. At the borders of the diseased area, there is some evidence of beginning cicatrization. The consistency of the process shows a rather firm tissue, which does not give much pain when the patient is unaware that it is being manipulated. *Right inguinal region:* An elevated scar in practically the identical position as the opposite side, 5 centimeters in length and 0.5 centimeter in width. At the inner end of this cicatrix is an active condition as above noted, circular in form and in size, one-half the area of a dime. *Vulva, perineum and nates:* The entire left labium majorum is covered by this granular tissue, and the opposite labium shows only a very small area of healthy and intact skin. The labia minora are moderately involved, as is the lower part of the vaginal wall. The granulations are continuous onto the perineum on the right side of the cleft, extending as far back as the anus. The vulva is much hypertrophied, the surface is nodular, moist, raw beefsteak appearance and bleeding at various points; the color is reddish, the odor offensive, the border sharply defined from the healthy skin and seripiginous in outline. The tissue has a firm feel and does not cause patient any discomfort when manipulated with moderate care. At the junction of the thighs and the vulva, the condition is present on the limbs, extending only where the vulva comes in contact with the thigh.

Laboratory notes: January 24, 1921, smear—gram positive bacilli; gram negative bacilli. Fontana stain—no spirochætæ. Giemsa stain—no granuloma bodies; no spirochætæ; few polymorphonuclear and mononuclears. Cultures—staphylococci, diphtheroids, streptococci, and a large gram positive encapsulated bacillus (unidentified). January 28, 1921, smear—gram stain—gram positive bacilli and diplococci. Gram negative bacilli. Cultures—plate overgrown with bacillus proteus. Smears show gram negative bacilli, staphylococci and diphtheroids. February 1, 1921, cultures on Sabouraud's medium show no growth after 72 hours. February 15, 1921, hæmoglobin, 70 per cent; red blood cells 3,470,000; white blood cells, 7,000; polymorphonuclears, 46 per cent; lymphocytes, 46 per cent; mononuclears, 3 per cent; transitionals, 3 per cent; eosinophiles, 2 per cent; marked anisocytosis, polychromatophilia, poikilocytosis. March 2, 1921, hæmoglobin, 40 per cent; red blood cells, 3,370,000; white blood cells, 6,600; polymorphonuclears, 45 per cent; lymphocytes, 49 per cent; transitionals, 2 per cent; eosinophiles, 3 per cent; basophiles, 1 per cent. Stipple cells, anisocytosis, polychromatophilia, and achromia. March 9, 1921, blood platelet count—410,000. March 22, 1921, fragility test—complete hæmolysis, 0.20; complete inhibition, 0.44. April 1, 1921, hæmoglobin, 55 per cent; red blood cells, 3,720,000.

Histopathology. Section from granulating area taken January 28, 1921, fixed in Schaudin's solution, stained with Giemsa's stain. Histological picture as above described. Smear stained with Giemsa's stain negative for encapsulated organisms.

Treatment. Treatment for granuloma inguinale was instituted January 29, 1921, the tartar emetic being prepared in 1 per cent solution in sterile water, beginning with a very small dose and increasing gradually each day until maximum dose was reached. January 29, 1921, injected 0.02 gram. No constitutional reaction; during the afternoon, the diseased area was itching continuously. No headache, nor pains in any of the bones of body. January 31, 1921, injected .025 gram. Three minutes following injection, patient complained of dizziness and sensation of fainting, but recovered rapidly; probably due to injecting the solution too quickly. She had a headache during the afternoon and evening, and considerable itching in the lesion. February 1, 1921, injected .03 gram. Drug injected a good deal slower than was done yesterday and no reaction occurred on the table. There is considerable itching beginning 4 hours following administration of solution, and stab-like stinging occurs every few moments, both lasting until about bed time. There is a great deal of secretion on the surface of the granuloma this morning, and the odor has become more marked. Patient complained of headache at vertex following the evening meal. February 2, 1921, injected .035 gram. The itching and stinging continue, commencing 3 or 4 hours after the injection. There was a good deal of pus-like material on the bandages this morning and much moisture over all of granuloma. February 3, 1921, injected .04 gram. Complains of itching and stinging in the lesion a few hours after injection. The solution causes a good deal of pain in arm and shoulder as it is being injected. Needle slipped out of vein and a bit of drug was injected into tissues; patient immediately cried with pain; hot water bag kept on arm all day. February 4, 1921, arm is slightly swollen and indurated at site of yesterday's injection, where solution went into tissues; very little pain and no sign of abscess. Complains of itching and especially stinging in the granuloma, the surface of which is very moist and bleeds extremely easy. There are several small white areas about the size of a small pea forming in various parts of the growth. At the edges of the healthy skin, new epithelium may be seen growing in over the granulation tissue. Dur-

ing the afternoon the patient complained of a severe backache. February 5, 1921, injection .05 gram. The whole surface of the granuloma is extremely moist, and the odor is very offensive. Considerable stinging is complained of locally. The serum or exudate from the growth stains the pad a pale yellow. February 7, 1921, injection .055 gram. February 8, 1921, injection .06 gram. Complains of itching and stinging, and a good deal of pain is present in the arm and shoulder when the drug is being injected. February 9, 1921, injection .07 gram. Does not note as much itching the last couple of days but the stinging does not abate any. Still complains of immediate pain and stinging up arm and shoulder as the solution is administered. February 10, 1921, injection .075 gram; February 11, 1921, injection .08 gram; February 12, 1921, injection .08 gram; February 14, 1921, injection .05 gram; February 15, 1921, injection .08 gram. Severe vertical headaches and the usual stinging; very little discharge and odor is lessening. There is a considerable amount of new epithelium making its appearance at the outer borders of the granuloma and around the small white patches that made their appearance the third day. February 16, 1921, injection .05 gram. Has had nose-bleed on three successive nights, but not severe. February 17, 1921, no especial complaint, patient is out of bed for past few days, the first time since admission in November. Her appetite and disposition have undergone a marked change for the better. February 18, 1921, injection .10 gram. February 19, 1921, injection of .11 gram. Epithelium is advancing daily and has covered a large portion of the granuloma; marked general improvement also. February 21, 1921, injection .11 gram. February 22, 1921, injection .12 gram. February 24, 1921, injection .08 gram. Changed from sterile water to normal saline to make the solution, and the pain in the arm and shoulder was not noticed by the patient, in fact she seemed to complain much less all the way through the day, than when the sterile water solution was used. February 26, 1921, injection .05 gram. The inguinal region has entirely healed and the vulva is rapidly approaching the normal once more. Injection .05 gram was given on the following dates: March 3, 8, 10, 12, 15, 23, 26, 29. The total amount of tartrate administered to date, 1.96 grams. The general condition of the patient is extremely good, appetite is excellent, excretions give no trouble, sleeps well, and irritability has disappeared. When she was admitted in November she weighed but 87 pounds; March 8, weight had increased to 99 pounds, and on April 21, a further increase to 106 pounds was registered. She had gained no weight up to the time the administration of tartar emetic was instituted. Three blood Wassermann tests November 11, 1920, December 27, 1920, and February 24, 1921, were all reported negative in all antigens. All urine reports have been normal; catheterized specimens were taken. April 23, 1921, received .10 grams of the drug intravenously, making the thirty-third injection. She has been discharged and will report to the venereal dispensary once weekly for continued treatment. The growth on the vulva and in the inguinal region has entirely disappeared, healing with considerable scarring, the cicatrix being slightly elevated. There are two or three small areas between the vulva and the thigh, and in the region of the fourchette that have not entirely healed, the largest of these is about the size of a dime. Patient followed to date (October, 1921). Has continued treatment as prescribed. No recurrence and has continued to gain in weight and general health.

CASE 3. G. J., male, negro, age 37, admitted May 19, 1920, complaining of sore in groin. Born in Virginia. Patient has traveled as a sailor to tropical ports. Seven years ago he had a sore on the foreskin. Several weeks later he developed a right-sided bubo, which was incised and drained. This healed without incident, broke down again 3 weeks later, but healed soon and has remained well since. Present condition started about 6 years ago, when there appeared two small pimples at the hair margin above the pubis and a little to the right of the mid-line. One of these healed up but the other enlarged and finally broke down, discharging some pus and rapidly forming exuberant granulations. This tissue spread throughout the right groin. Two years ago the entire growth was excised. The operative wound healed almost completely, except a small crusted center spot, and under this crust granulations again formed and began to spread. Soon the entire groin was involved and the granuloma extended down to the fold between the scrotum and the thigh on the right side. Six months ago X-ray treatment was begun and the condition has slowly progressed toward healing. February 10, 1921, patient is an employee of the hospital. The right groin and iliac region shows a large tense scar, part of which is devoid of pigment, extending from the symphysis to the iliac bone and measuring about 2½ inches in diameter. At the side of the scrotum the scar passes down the inguinal fold to the perineum, just posterior to the scrotum. At two places in this scar there are unhealed, active, lesions. One near the anterior superior spine, measuring 1 by 1½ inches in size. The granulation tissue over it is not exuberant, but lies flush with the surface of the skin, and is moist. (The effect of X-ray treatment.) The other area lies near the posterior part of the scar, in the fold between the scrotum and the thigh. This shows a sinus about one quarter of an inch deep, admitting only a probe point but discharging pus constantly. The area immediately around this opening is raw and abraded and shows an area of granulations about the size of a dime.

Treatment. On February 11, 12, 14, 15 and 16, 0.05 gram of tartar emetic was given intravenously. After the third injection, the upper lesion became dry and crusted over. The patient suffered some rheumatoid pains about right shoulder joint, painful to motion, but without local symptoms. Some of last injection was spilled into tissues. February 17, 1921, 0.08 gram of tartar emetic intravenously. February 21, 1921, abscess at point of injection where tartar emetic was given extravenously. Same incised. Given 0.08 gram today. February 25, 1921, 0.06 gram given today. Arm healed; upper lesion completely covered with epithelium; lower seems $\frac{1}{16}$ inch in depth and no exudate. On February 26 and 28 and March 2, given 0.06 gram of drug. March 3, 0.07 gram of tartar emetic intravenously. March 4, 0.08 gram of tartar emetic intravenously. March 7 and 8, 0.09 gram of tartar emetic intravenously. March 9, 16, 19, 23, 26, and April 11, 15, and 19 given 0.10 gram of tartar emetic. Patient has been under observation to date (October, 1921) without recurrence.

CASE 4. E. C., female, negro, admitted December, 1920, complaining of sores about vulva. Patient born in Virginia and moved in early life to Philadelphia, where she has lived ever since. Present condition started in August, 1918, with profuse vaginal discharge. In September, 1918, first noticed swelling in left groin which reached the size of a hen's egg. In October, 1918, several small pea-sized papules, grayish in color, were noticed upon left labium majorum and on the mons pubis. These itched and on breaking them exuded a watery material. They crusted over, did not heal, coalesced, and resulted in a moss-like, raw mass that bled on the slightest injury. She confesses to coitus 9 days before the development of these pimples. She was admitted to the Philadelphia General Hospital October 23, 1918, found to have Wassermann 1+. Given six injections of arsenobenzol, 14 intramuscular injections

Fig. 5 (at left). Case 1. Condition of patient on January 13, 1921. Groin, prepucial, and perineal involvement.   Duration 8 months.
Fig. 6. Case 1. Condition of patient April 23, 1921.   Lesions healed in 46 days. Has had 21 injections, total of 1.82 grams of drug. Note that scar tissue in the negro appears white.

of mercury salicylate (1 grain), and potassium iodide up to 150 grains daily and discharged on February 20, 1919, healed but with marked induration of right labium. She remained well for 1 year, but suffered a return of the original vulva sores in October, 1920, and was readmitted to hospital in December, 1920. Lesion described as follows: No evidence of bubo and groins free of disease; an elevated mass of granulation tissue covers the left labium, the mons pubis, and greater portion of right labium. Right labium markedly hypertrophic. The general appearance of the growth is pale red in color, with small bleeding areas at various points; the surface tends to be nodular, is shiny, and presents a moderate amount of moisture. There is no evidence of ulceration, the condition being elevated, proliferative, and with no sign of sloughing at any point. It is firm and gives but slight pain on handling. The lesion extends slightly onto the thighs where touching the enlarged labia. General condition of patient extremely poor, has lost at least 30 pounds in weight, appetite lost, strength gone and confined to bed greater part of time.

Laboratory notes. Section of tissue taken in December, 1920, reported: Chronic inflammatory tissue with areas of degenerated fibrous and epithelial tissue; not tuberculous. December 27, 1920, blood Wassermann test, 3+. December 30, 1920, blood Wassermann test, negative. February 24, 1920, blood Wassermann, negative. January 24, 1920, smears gram stain—gram positive diplococci and large bacilli. Gram negative diplococci and bacilli. Fontana stain—no spirochætæ or spirilla. Giemsa stain—no granuloma bodies. Cultures—diphtheroids and bacillus coli. January 28, 1921, smears—gram stain—gram positive bacilli and diplococci, gram negative bacilli. Giemsa stain—no granuloma bodies or spirochætæ. Cultures—overgrown with bacillus proteus. February 1, 1921, cultures on Sabouraud's medium no growth after 72 hours. February 9, 1921, smears—positive for granuloma bodies; stained with Wright's and Giemsa and showed many intra- and extracellular organisms, diplococci, and encapsulated. February 15, 1921, hæmoglobin, 50 per cent; red blood cells, 3,820,000; white blood cells, 9,200; polymorphonuclears, 46 per cent; lymphocytes, 43 per cent; mononuclears, 4 per cent; transitionals, 5 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent; marked asinocytosis, polychromatophilia, achromia, and poikilocytosis. March 2, 1921, hæmoglobin, 30 per cent; red blood cells, 3,450,000; white blood cells, 5,000; polymorphonuclears, 36 per cent; lymphocytes, 63 per cent (50 per cent

large) eosinophiles 1 per cent; polychromatophilia, asinocytosis, stipple cells, occasional normoblast. March 9, 1921, blood platelet count—380,000. March 22, 1921, fragility test: complete hæmolysis, 0.20; complete inhibition—0.46. April 23, 1921, red blood cells—3,380,000; hæmoglobin, 58 per cent.

Treatment. February 11, 1921, gram 0.03 tartar emetic given intravenously. February 12, 1921, 0.04 gram of tartar emetic given intravenously. February 14, 1921, 0.05 gram of tartar emetic intravenously. February 15, 1921, 0.06 gram of tartar emetic intravenously. February 16, 1921, 0.07 gram of tartar emetic intravenously. February 17, 1921, 0.08 gram of tartar emetic intravenously. On February 18, 19, 21, 22, 23, 24, and 26, was given dose of 0.08 gram; on February 28 and March 1, this was increased to 0.10 gram. On March 3, 8, 10, was given 0.08 gram and on March 12, 15, 18, 20, 23, 26, 30, and April 5 and 12, 0.05 gram were given. On April 20, 22, was given 0.06 gram. Total of 1.90 grams administered in 29 doses. Reactions from the drug never amounted to more than local stinging, itching, and throbbing in lesion immediately following injection. No generalized symptoms of toxic effects of drug. The granuloma has almost entirely disappeared except for a very small area in right labium that seems resistant and extremely firm. Healing was fairly rapid, leaving a slightly raised scar and markedly indurated labia. Patient's general condition greatly improved, appetite excellent, sleeps well, works about ward all day and has gained 25 pounds in weight. She is to receive 6 to 8 further injections and then be discharged to Out Patients Department.

CASE 5. H. J., male, negro, age 24, admitted February 22, 1920, complaining of a large sore in left groin. Patient was born in Maryland. Lived all his life about Baltimore, Centreville, and Philadelphia, never further south or outside of the country. Onset of the present condition was 3 years ago, when patient developed two small "pimples" on the inner surface of the foreskin. These remained for some time, and gradually increased in size, later breaking down and spreading slowly around the entire foreskin. Several weeks after these "pimples" appeared the glands in both groins began to swell. They receded under iodine treatment, later returned, receded a second time and about 6 months later became large and required incision. Following the drainage the right groin healed. The left, when almost healed, developed "proud flesh" and started to spread down the groin and into the fold between the
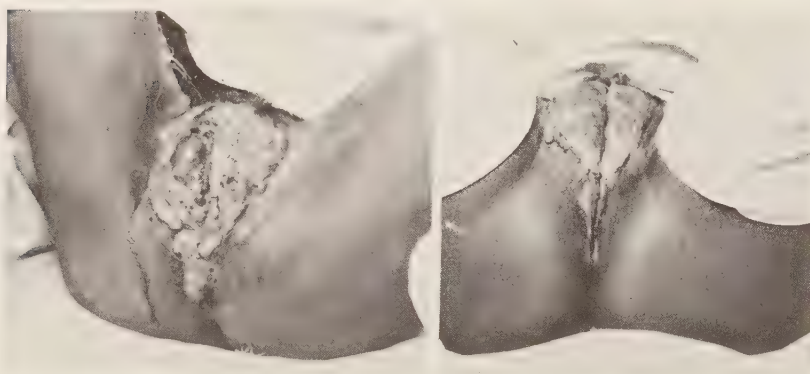
Fig. 7 (at left). Case 2. Pitiable condition of patient on January 28, 1921. Was not expected to live. Duration 3 years and this the third recurrence.

Fig. 8. Case 2. Result of 32 doses, totalling 1.96 grams of tartar emetic. Picture taken April 23, 1921. Lesion entirely healed in 59 days. Some induration remaining. General condition normal. Gained 19 pounds in weight.

thigh and scrotum. Over the perineum and about the anus, "bumps" appeared, which later broke down and coalesced. At present, in the region of the left inguinal glands at the seat of the old scar of a bubo, is a grayish, elevated, granulating mass, extending down between scrotum and inner side of thigh to the perineum, where it spreads to the width of 2 inches in diameter. It is sharply defined and is a constructive growth involving only skin surface, but in the region of the perineum a large ulcer is making its way into deeper tissues. Foreskin is long and can be retracted, and there are several granulating masses, resembling those in the groin, on the mucous membrane of the foreskin. NOTE.—This patient entered the hospital one year ago. He has been receiving X-ray exposures once every 3 weeks. Wound today (February 11, 1921) extends from within 1.5 inches of the left anterior superior spine, downward along the groin and scrotum to the posterior margin of this structure, it crosses the natal cleft, and involves the greater part of the urogenital triangle. The edges are raised and indurated and show evidences of slowly proliferating epithelium. The center of the lesion is moist, oozing, and granulating. The entire process is quite painful, especially at night and when the patient walks he has to assume a stooped position with legs spread widely apart. There is considerable offensive discharge from the surface of the perineal granulations.

Treatment. Given 0.05 gram of tartar emetic on February 11, 12, 14, 15, and 16. There has been a marked decrease in the discharge and the perineal region is covered with dry crusts for the first time in one year. Epithelium is definitely and rapidly growing inward from the edges and several isolated areas are proliferating epithelium at the base of the scrotum. The raised granulations are lower and there is much less pain. Given 0.08 gram dosage on February 17, 18, 21, 22, and 23. He has had some soreness and stiffness in shoulders and back on the mornings after injections, that decreased after being up and about. Epithelium continues to spread inward from all edges, induration is less, exudate decidedly less, and pain progressively decreasing. Given 0.10 gram on Feb-
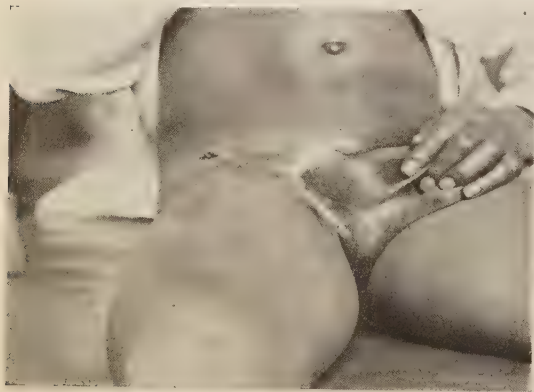
Fig. 9. Case 3. Old lesion of 6 years duration. Almost healed under persistent X-ray treatment. Picture taken January 13, 1921. Healed in 19 days. Patient has been observed to date (October, 1921) and so far has been without recurrence.
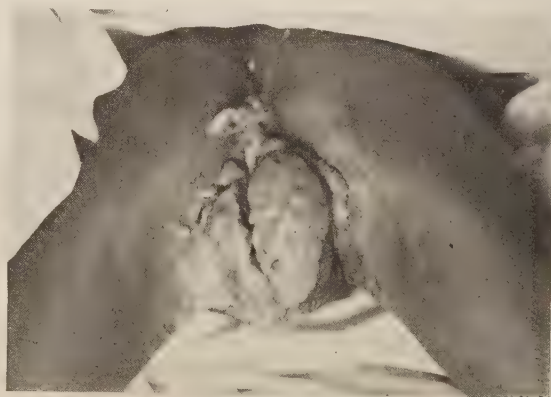
Fig. 10. Case 4. Condition January 28, 1921. This lesion is entirely raw, blood red, with extensions in left groin. Duration 3 years, and this is the third recurrence. Healed on April 23, 1921, after 29 doses of tartar emetic totalling 1.90 grams in 70 days. Labia remained markedly elephantic.
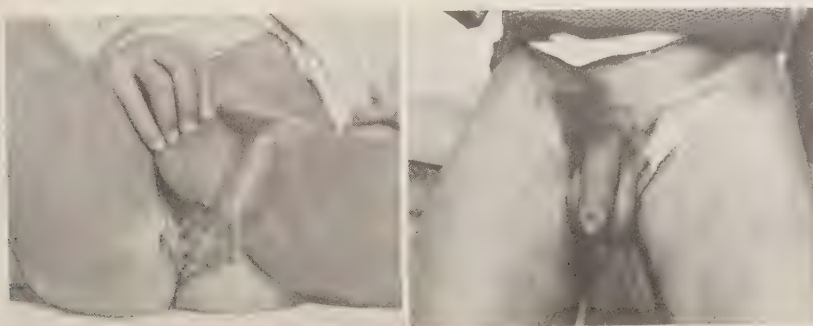
Fig. 11 (at left). Case 5. Condition of patient January 13, 1921. Lesion extending from anterior superior spine to anus. Patient could not walk up stairs. Duration 3 years.

Fig. 12. Case 5. Picture taken March 30, 1921. Lesions healed in 49 days. Has had 23 doses totalling 1.85 grams of tartar emetic. (Scar tissue appearing white.)

ruary 24 and 25. On February 26 was given only 0.06 gram because of persistent bone aches. On February 28 and March 3 dosage of 0.08 gram given. Note on February 27 states that for the past 2 days healing has become accelerated; perineal lesion is now half covered with epithelium; induration is progressively subsiding and patient feels quite well and can walk almost normally. Given 0.09 gram on March 4 and full dosage of 0.10 gram on March 7, 8, 9, 16, 23, 26, 31 and April 11, 15, 19, and 24. April 24, 1921, lesions are completely healed but treatment will be continued. Patient in excellent condition. Discharged today to the pay roll of the hospital as an employee.

CASE 6. W. F., male, negro, age 55, admitted February 26, 1921, complaining of growth about anus. Born in Pennsylvania where he has lived all his life. Unmarried and denies venereal disease. Present condition started a little over 2 years ago with slight bleeding, soreness, and distress when at stool. The proliferative growth has increased in size gradually and without recession until the present. There is no pain, soreness, itching or discomfort at present. Occasionally there is slight bleeding from prolonged work (porter) and friction of the parts. Appetite is good, bowels move daily, no loss of weight. On examination, external genitalia and groin are normal. The posterior raphé of the scrotum shows the beginning of a proliferative growth that forms two masses encircling the anus and completely filling the perineum and intergluteal region. The surface is made up of "tubercles" of new-growth, each about the size of a pea and the surface of each is covered with a pearly head of white epithelial tissue. It is painless, and is bathed in a slight serosanguinous secretion. The anal orifice is invisible.

NOTE.—This patient was admitted to the dermatological ward, where he was given three intravenous injections of neoarsphenamine (gram 0.90). His Wassermann twice taken was negative and no improvement in the local condition was observed. At our suggestion he was given one injection of tartar emetic, 0.05 gram and then transferred to our wards.

Laboratory notes. February 1, 1921, smear from lesion—negative for granuloma bodies. Cultures on Sabouraud's medium negative after 72 hours. February 7, 1921, smear from lesion—granuloma bodies present. No spirochætæ. Various bacteria. Cultures negative for Friedlaender-like bacillus. March 14, 1921, blood count—hæmoglobin, 55 per cent; red blood cells, 4,070,000; white blood cells, 10,800; polymorphonuclear, 71 per cent;

lymphocytes, 20 per cent; eosinophiles, 7 per cent; transitionals, 2 per cent.

Histopathology. Section from granulations. Fixation in formalin and Schaudin's solution. Stained with hæmatoxylin and eosin, and Giemsa. Typical of picture described. In addition there was marked proliferation of squamous epithelium in long processes possessing hyperchromatic cells. Section taken from granuloma, February 17, 1921, fixed and stained as above. Structure as above, except that there was no marked proliferation of the squamous epithelium. A few bipolar bacilli seen in endothelial leucocytes.

Treatment. Tartar emetic was given intravenously as follows: 0.05 gram March 2, 1921; 0.06 gram, March 4; 0.07 gram, March 7; 0.08 gram, March 8; 0.09 gram, March 9, with no reaction following injections. This patient has been perfectly tolerant to the rapid increase in dosage. He has not had any symptoms of reaction from the drug at any time. The lesion shows marked and rapid improvement, has decreased in size and especially flattened as though the new-growth was actually absorbing. The raw surfaces deep in the crypts between the proliferated tubercles have less discharge, and epithelization is progressing rapidly. 0.10 gram of drug was administered on the following dates: March 16, 19, 23, 26, 31, and April 11, 15, 19 and 23. April 23, 1921, patient has now received fifteen injections of the tartar emetic. He has shown no reaction to this drug save an almost complete disappearance of his granuloma. There are no raw surfaces remaining and the epithelium is smooth and healthy everywhere. Discharged under promise that he will continue weekly injections in the Out Patient Department.

NOTE.—Patient returned in September, 1921, with recurrence at ventral edge of anus. Had not kept up his Dispensary Treatment as advised.

CASE 7. B. A., male, age 43, admitted February 26, 1921, complaining of recurrent sore on penis. Patient was in hospital last year for the same condition which was relieved by X-ray. Born in South Carolina, but has lived in Philadelphia during the past 20 odd years, and condition developed while a resident of Philadelphia. The lesion appeared for the second time 2 months ago, as a simple "pimple" on the glans penis. This grew in size until as big as a finger nail, when it broke down and became an open sore. There has been no pain, no discharge of pus from it, but a continual oozing of bloody serum. It has increased in size very gradually. It appears as a sharply defined, raw area over glans penis and extending up about

Fig. 13 (at left). Case 6. Lesion limited to anal region and of 2 years duration. Picture taken January 21, 1921.
Fig. 14. Case 6. Result of treatment: Patient has received 20 doses totalling 1.07 grams of tartar emetic. Picture taken May 14, 1921. Healing complete in 37 days.

1 inch on shaft of penis, is not ulcerated, but covered with clean granulation tissue. The mucous membrane is destroyed, leaving a raw, red, oozing surface studded with tiny heads of granulation tissue. It is painless, odorless, and free of discharge.

Laboratory notes. March 1, 1921, Wassermann, negative. Smear positive for typical intracellular organisms. Urine analysis negative. Blood count: hæmoglobin, 82 per cent; red blood cells, 3,950,000; white blood cells, 7,650; polymorphonuclears, 57 per cent; lymphocytes, 36 per cent; mononuclears, 1 per cent; eosinophiles, 4 per cent; basophiles, 2 per cent. March 2, 1921, smears from lesion—positive for granuloma bodies. Cultures, negative for Friedlaender-like bacillus. March 7, 1921, smears from lesion—positive for granuloma bodies. Cultures, negative for Friedlaender-like bacillus. March 11, 1921, smears from lesion—positive for granuloma bodies. Cultures, negative for Friedlaender-like bacillus. Fragility test: complete hæmolysis, 0.28, complete inhibition, 0.40.

Blood platelet count, 247,000. March 12, 1921, smears from lesion, positive for granuloma bodies. Cultures negative for Friedlaender-like bacillus. April 4, 1921, smears from lesion, after four injections—negative for granuloma bodies. Cultures—negative for Friedlaender-like bacillus

Histopathology. Section from margin of lesion taken March 2, 1921. Fixation as outlined and picture typical of original description.

Treatment. Patient was given tartar emetic intravenously 0.05 gram March 23, 1921; 0.06 gram March 25;

Fig. 16. Case 8. Old lesion of 2 years duration. Almost healed with X-ray. Note double groin involvement and marked induration of foreskin. This induration was greatly reduced by treatment. Picture taken March 30, 1921, after 14 injections of tartar emetic and completely healed. Treatment has been persisted in, and there has been a decided diminution in the heavy induration of the foreskin.

Fig. 15. Case 7. Lesion of glans and foreskin only. Duration 2 months but this is a recurrence of a primary attack. Healed in 69 days with 10 doses totalling .85 gram of tartar emetic. Picture taken March 30, 1921, after third injection had been given.

Fig. 18. Case 12. Lesion of glans and foreskin only. Duration 4 years. Healed in 28 days with 8 doses of sodium antimony thioglycollate, totalling 0.68 gram of drug. Picture taken May 11, 1921, before starting treatment.

Fig. 17. Case 10. Condition of patient end of February, 1921. Duration one year. Healed in 42 days, having received 17 injections totalling 0.94 gram tartar emetic.

0.07 gram March 26, and 0.08 gram March 31. Patient has had some rheumatoid pains in shoulders and slight swelling of feet that has made caution necessary with medication. No alarming symptoms, and condition improving rapidly. On April 11, 1921, 0.09 gram of tartar emetic was given intravenously; April 15, 0.10 gram and the same quantity on April 19. Patient has a conjunctivitis and nasal congestion. Injection stopped. Lesion practically healed. On May 9, 23, and 31, 0.10 gram of tartar emetic was injected intravenously. Patient has had ten injections of the drug. Over the lesion on the foreskin a new epithelium has formed entirely; the glans penis is entirely healed except for a narrow sore on the back of the glans about ⅛ inch wide and ¾ inch long; this is dry, level with the remaining surface and apparently on the verge of complete healing. Patient up and about in good condition, wishes his discharge, and agrees to come to the dispensary for further injections.

CASE 8. W. H., male, age 39, admitted June 30, 1920, complaining of a sore in groin and inguinal fold. Has been living in Philadelphia for the 2 years prior to the onset of the present condition, which started about December 1918, with a sore on the base of the shaft of the penis. This was pronounced a soft sore and not luetic. It did not heal and about 6 months later the condition broke out in the right groin and has remained as an open lesion ever since. Patient is an unusually fine physical specimen of negro, of almost gigantic development. General physical examination is negative. Genitalia show a raw ulcerated area about the root of the penis and in the right groin extending down to the fold between the scrotum and the thigh. It is raised about the edges and of deep red color, not undermining, and free of discharge or odor. Patient was placed under X-ray treatment for "tuberculosis cutis," receiving exposures every third week. On June 30, 1920, improvement is noted. On August 23, 1920, condition recorded such that he is able to work and patient discharged from the ward to the payroll and put to work in the kitchen.

February 11, 1921. Physically, patient is in excellent condition except for lesions about genitalia. Here there is marked infiltration and scarification of the skin over the base of the penis, resembling elephantiasis. Foreskin is very indurated, hard, and painless; it cannot be retracted. On right inferiolateral aspect about the middle of the shaft is an oblong ulcerated area lying in the middle of a white, indurated, and painless scar. It is 1.5 by 1 centimeter in size, and of a raw, red color. There is a similar, but larger, area on the right side of the scrotum in the inguinal fold; it is moist, bleeds easily on manipulation, flesh is red in color, and is covered with a thin, purulent exudate.

Treatment. On February 11, 12, and 15, 0.05 grams of tartar emetic were given intravenously. Patient says sores are better than at any previous time. Both are covered with a light crust, perfectly dry and epithelium is commencing to proliferate. On February 16, 1921, 0.05 gram of tartar emetic was injected intravenously; on February 17 and 18, 0.08 gram. The lesions are much smaller and induration seems softer. On February 21, 1921, 0.08 gram of tartar emetic was given intravenously. Ulcer on penis healed today. On February 23, 1921, 0.08 gram of tartar emetic was given intravenously and on February 28, 1921, 0.10 gram. Induration of foreskin is rapidly disappearing. The ulcer in groin is scabbed over and apparently healed though not disturbed. Patient has not had any reaction to the medication at any time. Treatment persisted in and on the following dates 0.10 gram of tartar emetic was given: March 2, 3, 4, 7, 8, 9, 16, 19, 31, and on April 11 and 19.

NOTE.—October, 1921. It is of interest to note that treatment has been so satisfactory to the patient that he persisted in its administration long after he was healed with the result that there has been a marked decrease in the heavy elephantic induration of the skin and foreskin of the penis.

CASE 9. W. P., male, age 26, admitted April 28, 1920, complaining of a sore in left groin. In August, 1919, he contracted a sore on the penis and some time after a generalized eruption. In the last 2 weeks he developed enlarged glands in the left groin, which were opened 1 week ago and have been discharging since. There is also a sore on the penis that has been present for the past 4 weeks. With the exception of scars from sinuses and indurated glands of neck, and evidence of infiltration of both apices, general physical examination otherwise negative. There is a phimosis with slight purulent discharge from foreskin. In both inguinal regions are large masses of lymph glands densely matted together, while on the left is a particularly large mass with sinus formation from which pus exudes. Patient was circumcised at this time
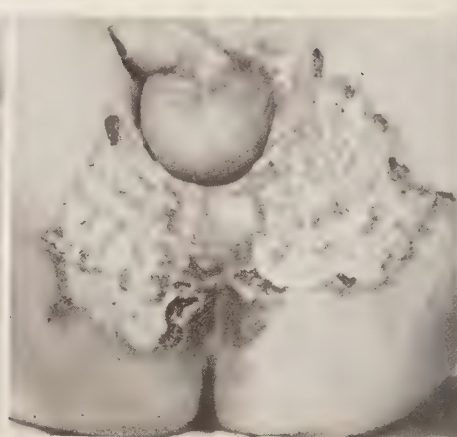
Fig. 19.   Fig. 20.   Fig. 20.

Fig. 19. Case 14. Picture taken April 12, 1921. Duration 7 months. Patient has received all forms of local antiseptics and dressings, without benefit. Has had repeatedly negative Wassermann tests, but nevertheless, was first given intensive antiluetic treatment during following 3 months and showed no improvement.

Fig. 20. Case 14. Picture taken September 16, 1921, after persistence on tartar emetic injections over 6 weeks. Dose of 0.06 gram was given every 2 days, and he is still undergoing treatment. In all probability he has had a double infection.

(April, 1920) and given 8 doses of neosalvarsan, and on August 24, 1920, he was healed and symptomless (except as noted below) and was then placed on the pay-roll of the Institution.

February 2, 1921: This man is an employee at the firemen's and officers' mess. He has been kept in the institution in order to receive X-ray treatment every 3 weeks, for unhealed condition in groins considered at the time to be tuberculosis cutis. His general physical examination is negative, he is well nourished and developed and apparently in good health. The lesions in the groins have slowly cicatrized with the exception of an ulcer at the base of the scrotum on the right side about the size of a kidney bean, and on the inside of the left thigh, where it comes in contact with the scrotal lesion, are found four raised areas, sharply defined, plateau-like, about 1½ centimeters in size. These latter lesions are covered by very thin epithelium and on two of them where the epithelium has been rubbed off typical granulation tissue is present. Patient states they are new lesions beginning to develop, as others have done before.

Treatment. On February 2 and 12, 1921, 0.05 gram of tartar emetic was injected intravenously; on February 18, and on February 28, 0.10 gram.

April 11, 1921, patient healed so rapidly after above treatment that he neglected his injections. Today there is a recurrence of similar lesions on the thigh. He was given 0.10 gram of tartar emetic intravenously. April 19, 1921, 0.10 gram of tartar emetic intravenously.

NOTE.—This patient is an employee of the hospital. He has persisted in his treatment and has remained perfectly healed to date (October, 1921).

CASE 10. M. W., female, age 20 (from the service of Dr. A. H. Lippincott, Cooper Hospital, Camden, New Jersey), admitted February 8, 1921, presenting extensive lesions about genitalia. Past history unimportant. Present condition of 1 year's duration, commencing as a small nodule on the right labium majorum, which ruptured and then started to proliferate, and has gradually involved the entire vulva and perineum. The rapidity with which this

extended varied, but at no time did it show any tendency to heal spontaneously, and patient has not received any medical treatment for the condition. There has been a rather constant, profuse, foul-smelling, and at times blood-tinged discharge. Chest examination showed evidences of pulmonary tuberculosis at both apices. The vulva lesion presents a large, raw mass covering both labia, and extending from the symphysis to the perineum, it follows the labia down into the vagina and extends into the anus posteriorly for about 1.5 inches. Cystoscopic examination is negative. Histological examination was made of section of tissue removed from the right labium. At the same time smears were taken from the area of excised tissue. Microscopic examination showed a marked round-cell infiltration. Polymorphonuclears and a few eosinophiles can be seen. There are some infolding areas of epithelium. No evidence of malignancy. Smears from lesion were positive for granuloma bodies. No cultures were taken. Blood count, hæmoglobin, 69 per cent; red blood cells, 2,100,000; white blood cells, 9,600; polymorphonuclears, 85 per cent; lymphocytes, 10 per cent; large mononuclears, 4 per cent; eosinophiles, 1 per cent.

Treatment. From February 10 to March 7 local treatment with the usual surgical dressings and applications produced no result whatsoever. On March 7, 1921, she was given 0.05 gram of tartar emetic intravenously, and noticed intense burning pain in the lesion immediately after administration, lasting about 10 minutes. On March 9, this dose was repeated and on the 11th and 13th 0.06 gram was given. After this fourth dose, evidences of healing appeared about the edges of the granuloma over the symphysis. Gram 0.06 was given on March 18, 21, 23, 25, 28 and 30, at which time it was seen that the condition, at first slowly healing, was now healing with great speed and rapidly being covered with epithelium. Same dosage was administered on April 2, 4, and 8 when her hæmoglobin was found to be 70 per cent and red blood cells, 3,000,000. Healing still progressed rapidly, and after injection of the same dosage on April 11, 15 and 18, the entire lesion was healed except for a small area to the

right of the anus and a heavy subcutaneous induration of the labia. Patient discharged. To continue treatment in Out Patients Department.

CASE 11. G. W., male, negro, age 25, admitted July 13, 1921, complaining of open sore in the right inguinal region. He had a chancre 4 years ago and gonorrhœa 3 years ago. This present condition was preceded by a bubo which broke down spontaneously and then healed. Upon the scar a new lesion appeared which has persisted for three years. Patient in wretched condition and health. Abdominal wall and thighs studded with keloids, scars and abscesses from the use of hypodermic injections. In the right inguinal region is a raw granulating surface typical of the granuloma lesion and 10 by 4 centimeters in extent.

Laboratory notes. July 18, 1921, smears from lesion, positive for granuloma bodies. Cultures, negative for Friedlaender-like bacillus.

Treatment. Tartar emetic was given intravenously as follows: 0.05 gram, July 15, 1921; 0.06 gram, July 17; 0.07 gram July 19; 0.08 gram July 21; 0.09 gram July 23, and on July 25, 27, 29, and 31, 0.10 gram.

Final note. The granuloma is very much improved and is healing along upper edges. Patient insists on being discharged against our wishes. He is a drug addict.

CASE 12. E. P., male, age 32, admitted May 5, 1921, complaining of sores on penis of 4 years duration following a slight "hair-cut" in the skin of the frenum. This slowly became sore and inflamed, and at the end of 1 year presented two sores each about the size of a finger-nail. Was given, a year ago, about twelve injections of neoarsphenamine with slight improvement but not complete healing, and during the past 2 months the lesion has shown greater activity and growth.

On examination the foreskin was found swollen, œdematous, and almost covering the glans. On the glans about the meatus and on the mucosa of foreskin on either side from frenum are sharply defined, firm, raw, red, oozing areas with slightly elevated borders. Wassermann reported 2+ and patient given three injections of neoarsphenamine, after which sore reported "drier, no oozing and cleaner, but no closing in of the edges, no islands of skin formation, i. e. no healing."

Laboratory notes. Smear from lesion—positive for granuloma bodies. Culture, negative for Friedlaender-like bacillus. Blood culture, sterile. Blood Wassermann, 2+; cholesterin, 4+; noguchi, 1+. May 7, 1921, smears from lesion, positive for granuloma bodies, culture, negative for Friedlaender-like bacillus. May 9, 1921, complement fixation using antigens made from organisms from Case 16, Case 14, and Friedlaender-like bacillus from sputum. Results—all negative. Smears from lesion—positive for granuloma bodies. Cultures negative for Friedlander-like bacillus. May 14, 1921, inoculation of patient. Two abraded areas were made on the left arm; one was inoculated with cotton swab saturated with a 24-hour culture of the Friedlaender-like bacillus isolated from Case 16; the other with normal salt as a control. Patient was kept off of specific antimony treatment until May 31, 1921. Observations were last made on June 29, 1921, and up until this time no lesion had resulted. May 26, 1921, smears from lesion, negative for granuloma bodies; culture, negative for Friedlaender-like bacillus.

Histopathology. Section from granulations taken May 6, 1921. Fixed and stained as described. Picture that of original description. Very little proliferation of epithelium from skin. A few intracellular coccoid forms suggest granuloma organisms, minus their capsules. They are seen only in the large mononuclear cells.

Treatment. May 31, 1921, first injection of sodium antimony thioglycollate intravenously — 0.05 gram intra-

Fig. 21. Case 15. Picture taken January 28, 1921. Duration 6 weeks. Wassermann 4+. Given neoarsphenamine and X-ray exposures for 5 months with only partial healing. Cured with five injections of tartar emetic.

venously; on June 2, 1921, 0.06 gram; on June 6, 1921, 0.07 gram; on June 10, 1921, 0.10 gram; on June 13 and 16, 1921, 0.10 gram; on June 24, 1921, the lesion is healed. One area is covered with superficial scab. On June 24 and 27, 1921, 0.10 gram of tartar emetic was given intravenously. July 1, 1921, lesion is entirely healed. Discharged from ward. To continue weekly injection of tartar emetic in venereal dispensary.

CASE 13. D. H., female, admitted May 30, 1921, complaining of genital sores of one year duration, whose onset followed several boils upon the buttocks and started as an itching papule upon the labia majora and spread as a raw, oozing, red surface.

Examination reveals the labia majora as big, hypertrophied, swollen-looking affairs. Beginning with the inner margins, the labia are ulcerated, the ulcerated proliferating mass of tissue taking in both labia majora and minora on both sides and extending from the anterior part of the labia minora to the posterior parts in both sides. This mass is very hard, granular looking, with here and there a white plaque-like looking area. It is red but not bleeding. When touched or rubbed it does not bleed and very little pain is complained of. There is no odor. The mass extends to the entrance of the vagina, and here ends quite abruptly. The vaginal wall is not inflamed but feels quite hard. The cervix is not eroded and the cervical canal is normal. There is very slight discharge. No masses can be felt by vaginal examination. The uterus seems to be slightly posterior. There is no cystocele, rectocele, or vaginal fistulæ.

Laboratory notes. June 1, 1921, a section taken from margin of lesion, fixed, and stained as described, shows typical histological picture of granuloma but no intracellular organisms were found. June 3, 1921, smears from lesion positive for granuloma bacillus. Cultures, negative for Friedlaender-like bacillus. June 13, 1921, smears from lesion positive for granuloma bodies. Cultures, negative for Friedlaender-like bacillus. Some material directly from the lesion put into broth, centrifuged, and the sediment inoculated into animals. Three guinea pigs and a mouse were inoculated subcutaneously. No lesions occurred in any of the animals.

Treatment. Between May 20, 1921, and June 23, 1921, patient was given six (6) intravenous injections of 0.05

Fig. 22. Case 16. Picture taken on admission to Penitentiary, June 29, 1920. Lesion of 10 years' duration. Condition approximately the same when tartar emetic treatment started May 5, 1921. Healed in 45 days after 20 injections of tartar emetic.

gram each of tartar emetic. Between June 25 and July 26 patient was given four (4) injections of 0.08 gram each and three (3) injections of 0.10 gram each of tartar emetic. Between August 1 and August 22 (day of discharge), patient was given seven (7) injections of 0.08 gram each of tartar emetic.

On date of discharge, August 22, condition so thoroughly healed, that she was discharged to Out Patient Department to continue after-treatment. She has been working around the ward for the past month, has no complaint, and has gained in weight.

CASE 14. F. D., male, *white*, age 25, admitted December 20, 1920, with excoriated sores about left groin and perineal region. Onset 2 months before with four or five sores on the penis. These primary lesions were soft, painful, and like fever blisters and were followed by an inguinal adenitis which became "ripe" and a doctor opened the abscess. It slowly but completely healed, but shortly after healing multiple sores broke out about the edges of the inguinal scar. These sores have received abundant attention and many local applications but have progressively spread until on admission the lesion extends down the side of the scrotum and thigh, over the perineum, and as far back as the anus and cheeks of the buttocks. Wassermann negative with three antigens; von Pirquet skin test for tuberculosis negative. There was great divergence of opinion among the staff as regards the diagnosis in this, the only white man in whom the granuloma bodies were found. First considered chancroidal, he was given local treatment; next as tuberculosis, X-ray was tried; in April the finding of typical intracellular organisms of granuloma inguinale started him on tartar emetic therapy and when no improvement was noted after eight injections, it was ordered off and a fourth opinion instituted active antisyphilitic treatment which was pushed for 2 months without any apparent improvement. Beginning July 26, 1921, patient has been getting on alternate days intravenous injection of 1 per cent tartar emetic. Started with 5 cubic centimeters and advanced to 10 cubic centimeters then dropped to 6 cubic centimeters per dose. Condition fluctuates. Heals almost and then breaks down anew. Now healed more than ever before and only a periphery of superficial and not particularly inflamed ulcerations left. Patient's general condition excellent.

NOTE.—This is the only case that we have experienced of infection in the white race. The picture was not typical and our feeling is that a double infection was probably present. He received vigorous antiluetic treatment to no avail in the face of repeatedly negative blood tests. His improvement under antimony has been more marked and permanent than anything during the previous 7 months. Picture shows the amount of improvement, patient at this date under continued antimony treatment. General physical condition has improved very markedly.

CASE 15. B. B., female, age 20, admitted December 29, 1920, complaining of sores on genitalia and in groins. Onset 6 weeks before admission, as small papule on right labia. Patient picked this sore and one week later it started to increase in size and has refused to heal. Lesion found to involve left inguinal region, both labia, the right being ulcerated its entire length as likewise the right labia minora with extensions to entrance to vagina. Wassermann 4+ on all three antigens. Patient given two injections of neoarsphenamine and discharged to Out Patients Department where treatment with neoarsphenamine was continued at weekly intervals until June 1, 1921. She likewise received X-ray exposures at 3-week intervals. Readmitted on above date and local condition found somewhat improved, the labia of elephantic size and the lower half of right labium still an open sore.

Laboratory notes. June 3, 1921, smears from lesion, negative for granuloma bodies; cultures, negative for Friedlaender-like bacillus. June 6, 1921, smears from lesion, positive for granuloma bodies; cultures, negative for Friedlander-like bacillus.

Treatment. July 14, 1921, patient has received one (1) injection of 0.05 gram of tartar emetic and four (4) injections of 0.08 gram tartar emetic. Lesion is now entirely healed. Most of the induration has gone and patient is today discharged to Out Patients Department for continuation of treatment.

CASE 16. C. B., male, age 43. Patient's first admission was in 1911, suffering with a sore involving foreskin and glans. Eight years before (1903) he had had a similar lesion which healed in 4 weeks and again 3 years before (1908) a second lesion on foreskin at which time he was circumcised and it took 10 months to heal. Present sore developed 1 year after the above second lesion and has had various

treatments during 2 years without any apparent effect toward healing. He remained in the hospital for 1 month and was discharged (on request) unhealed. Readmitted in 1915 with lesion showing destruction of skin and sub-cuticular tissues over entire penis and extending over upper portions of scrotum, into groins and suprapubically. Received active antiluetic treatment and 8 X-ray expos-ures. Diagnosed tuberculosis cutis and discharged 7 months later still unhealed. Readmitted in 1916. Penis almost completely destroyed and scrotum markedly swollen. Condition has gradually and continually grown worse. Similar diagnosis and treatment instituted and dis-charged 3½ months later, with condition somewhat re-lieved. Readmitted in 1917. Penis completely destroyed. Ulceration extending over right inguinal region and upper portions of scrotum. Received 18 X-ray exposures and discharged 10 months later.

NOTE.—Patient known to be at present an inmate of the penitentiary which he entered on June 29, 1920. Investigation found him to be in about the same condition as at the time of his fourth hospital admission as revealed in the picture taken at the time of his confinement. July 20, 1920, Wassermann test, negative. August 20, 1921, following letter received from Dr. H. Phillips, resident physician, Eastern Penitentiary, Philadelphia, Pennsyl-vania: "In accordance with your request we submit below data on C. B., a prisoner now confined in the above institu-tion. On May 5, 1921, we commenced intravenou traeat-ment. Injection 5 cubic centimeters, 1 per cent tartar emetic, gradually increasing dose until 10 cubic centimeters was given in each injection. These injections were given every other day for a period of 2 months. Afte r2 months the treatment was cut down to one injection weekly. After ten treatments were administered he began to heal very rapidly, and was entirely healed after being under treatment for a month and a half. Following is list of treatments as given: May 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31; June 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30; July 2, 4, 7, 14, 21, 28; August 4, last injection. Trusting this will cover the information desired."

Laboratory notes. April 26, 1921, smear from lesion—positive for granuloma bodies; cultures, positive for Friedlaender-like bacillus.

Histopathology. Section from margin of granuloma, fixed and stained as others. Structure typical of granuloma. Large preponderance of endothelial cells. Considerable proliferation of squamous epithelium. Coccoid forms seen in some large mononuclear cells.

BUBONIC PLAGUE: ITS PREVALENCE IN THE UNITED STATES AND HOW THE DANGER SHOULD BE MET*

EDWARD B. KRUMBHAAR, M.D.

PHILADELPHIA

To the average doctor "bubonic plague" recalls indistinct memories of the Black Death of the fourteenth century, De Foe's account of the Plague of London in 1665, perhaps Thucydides' description of the Plague of Athens during the Peloponnesian War, or Biblical references to sudden death amid a plague of rats and similar "far off things of long ago." Little does he realize that for the past 26 years practically the whole world has been suffering from a pandemic that has caused literally millions of deaths and will undoubtedly take rank in history with the devastations just referred to. Inasmuch as the U. S. Public Health Service is confident that this country will continue to be exposed to the introduction of epidemics for at least another 50 years, a closer view of the present pandemic becomes highly advisable.

From the fourteenth to the seventeenth centuries the civilized world was frequently visited with epidemics of the plague of greater or less severity, but since that time the infection has remained relatively quiescent in endemic foci in Asia with occasional outbreaks in Europe as late as 1870. In 1894, a plague epidemic reached "dangerous proportions" in Canton and Hong Kong, although sporadic cases had been known in various locations in southern China for at least 25 years before that. With a total

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in the thousands,‡ the epidemic was soon car-
of several thousand deaths in Hong Kong and
a weekly mortality in Canton that was measured
ried by shipping to Bombay and Calcutta,
whence it spread overland in truly appalling
proportions and its ravages have continued
throughout India until the present day. Ac-
cording to Sir Bromwell Leslie,† the total num-
ber of deaths in the Punjab alone for the first
half of 1907 was not less than a half million, so
that the estimate of over a million deaths in
India during the present pandemic may be con-
sidered conservative. With India and China as
the chief endemic foci, plague has spread
throughout the civilized world, so that epidemics
or sporadic cases have been observed in the
past decade in practically every country of
Europe and America. In Manchuria, starting
from the marmot, human cases became infected
with the pneumonic type of plague, which
spread so rapidly along the railroads and other
inland lines of communication that in 10 weeks
there were over 50,000 deaths. This epidemic
is of particular interest to us in the northern
states as an example of the pneumonic type of
plague that is especially prone to attack colder
regions, and also as a demonstration of the pos-
sibilities of overland transmission of this dread
disease. In this epidemic, as is usual in pneu-
monic plague, the mortality was practically
100%. Our own plague experiences from 1907
to 1914 in Porto Rico, Havana, New Orleans,
Seattle and San Francisco are, I hope, sufficient-
ly familiar to you to render further comment un-

‡This epidemic was also noteworthy not only for the cus-
tomary observation of a great coincident mortality among rats,
but also for Kitasato's discovery of B. Pestis in 1894, and of
the flea transmission of the infection by Ogata in 1896.
†Report of Board of Health on Plague in New South Wales
in 1907, p 53, Sydney, 1908

necessary, but perhaps it is not so widely known that in the past year separate outbreaks that total in the hundreds have occurred in Mexico, Paris, Fiume, and our own Gulf States.

In Seattle and San Francisco, due to the energetic action of the U. S. Public Health Service, coöperating with the local authorities, plague has apparently been eradicated from both the human and rat population, although in California it was found among rats at least eight months after the last human case, and has become endemic and apparently ineradicable among the ground squirrels. In New Orleans, the epidemic was found persisting among rats eleven months after the last human case, and in spite of the continuance of anti-plague measures, human plague broke out again in that city in October, 1919, after an apparent freedom of over two years. In spite of anti-plague measures of the most approved type, human cases are still occurring there, and it is not perhaps an exaggeration to state that the situation was brought under control within two months and any noteworthy spread of the infection prevented largely by means of the rat proofing measures that had been accomplished there in the previous six years. Since October, 16 human cases have occurred with six deaths (September, 1920). During the same period over 300,000 rats have been trapped and examined and about 600 found to be infected with plague. And all this in spite of the fact that several million dollars had been spent in rat proofing most of the city and all but five of the five miles of river docks.

In Galveston, the first case of plague was recognized on June 6th of this year, since which time there have occurred 12 cases with nine deaths. In Beaumont, Texas, the first human

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case was observed on June 26th, since which time there have been 12 cases with five deaths. Although the source of these epidemics has not been definitely traced, it was probably due to shipping transmission in both instances. For several months before these outbreaks, it had been observed that the rats of the locality were dying in unusually large numbers, and when rat surveys were undertaken, it was found that as high as 20% of the rats caught or found dead were plague infected. Following anti-plague measures this percentage was quickly reduced, until for the week preceding the visit of the Plague Conference in August, no plague infected rats had been found.

Although the Galveston outbreak preceded that of Beaumont and was apparently less widely distributed at its onset, it has not been as well controlled on account of less successful coöperation of the citizens with the state and federal Public Health Services. In Beaumont, not only were both a special plague laboratory and isolation hospital quickly established with adequate trapping, rat proofing and wrecking squads and inspectors, but a special ordinance was passed giving the health authorities full authority to disinfect, survey and condemn all infected or rat-harboring structures. If they were not demolished or made satisfactorily rat-proof within 30 days of notification, the structures could be demolished or made rat-proof by the health authorities at the owner's expense.

In the light of these and similar experiences elsewhere, how then should the plague danger be met, not only where it has actually gained a foothold, but where it may at any time in the near future be introduced (in other words, in any seaport of this country)? From an epi-

demiological standpoint, the case of human plague is a mere incident, "the innocent by-stander who is hit by the brick." All energies and resources should therefore be devoted to fighting the rat, whose flea is responsible for the transmission of the plague, not only to rats and other rodents such as ground squirrels, but to man as well.

Anti-plague measures may be divided into the
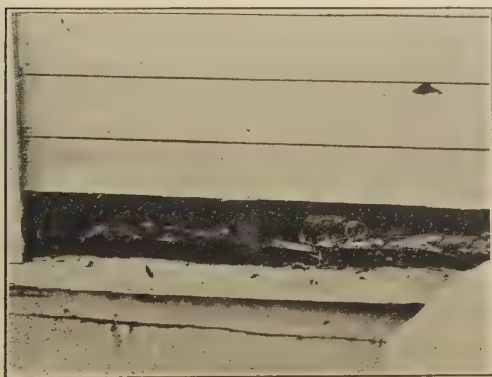
Fig. 1. Exposed rat harborage between double walls of frame dwelling house. Showing nest and accumulation of several years débris.

following categories: (1) "rat-proofing", (2) rodent extermination, (3) rat survey, (4) treatment of cases, (5) research work.

(1) *"Rat-proofing."* By far the most important measure in the prevention of plague is the process of "rat-proofing," i. e. rendering a locality (houses, barns, sidewalks, yards, storehouses, docks, shipping, station, freight cars, etc.) unfit for the harborage of rats. This term does not imply, nor is it necessary, that rats cannot gain entrance to or exist in rat proof buildings; but it does indicate that conditions

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for existence and reproduction are so unfavorable that the few rats that do gain entrance will soon leave for more favorable surroundings. That "rat-proofing" is important in the eradication of plague, as well as in its prevention, is shown by the strenuous and strikingly successful measures adopted by the U. S. Public Health Service in coöperation with the local health authorities during the past 15 years. The most important item in "rat-proofing" is the safe guarding of buildings, either by concrete floors and "chain walls" (class A), or by elevation of house at least 18 inches from the ground and maintenance of this space free from rubbish. Incidentally, in New Orleans the economic gain of rat-proofing was soon demonstrated to be so great that the larger corporations willingly coöperated in rat-proofing measures that involved an expenditure of thousands of dollars on their part. This economic gain comes from not only a diminution in claims for damage by rats to the merchandise handled, but also to greater efficiency in handling same through less wear and tear to the building, to the trucks, etc., and to the ability to move goods over the smooth surface of the concrete floors more rapidly and with less labor. Coincident with the rat-proofing of buildings, sidewalks, etc., all other factors favoring rat existence should as far as possible be eliminated. This includes such details as the proper protection of foodstuffs and feed bins, and the proper disposal of garbage, manure and rubbish. It is obvious that such measures are also highly desirable from a general sanitary as well as a specific anti-plague standpoint.

Another important item in rat-proofing a locality is to prevent the entrance of foreign rats

from shipping. The measures commonly used are: (1) Three foot funnel-and-disc rat guards on all hawsers, (2) "breasting" the ship at least 15 feet from the dock by means of suitable rafts, and (3) loading or unloading only by daylight or with strong artificial light, the gangplank (at least 10 feet of which is painted white) being lifted at all other times. Even these measures are not absolute protection (for instance, against overhanging sheds or other structures on the dock) and lose greatly in efficiency unless supported by a strong inspection force and the public opinion of the community. For instance in New Orleans to-day (September, 1920), many of the ships have rat guards for three-inch cables placed on one-inch ropes, have omitted the "breasting" or left the gangplank down all day and unguarded. Although introduction of rats by inland freight is undoubtedly of minor importance, it should be guarded against by inspection and opening of double walls of freight cars at least one foot from the floor.

(2) *Rodent extermination*. In the presence of human plague or of the epizootic in the rats of the locality, rodent extermination assumes primary importance. This is best accomplished by means of trapping and fumigating (especially for ships and freight cars) although it has never been possible to render a locality entirely rat free; and even if this were possible it would quickly become more or less infested under conditions existing to-day. In fact, it is recognized that even an extensive campaign of extermination is only of temporary benefit (unless accompanied by rat-proofing) because the greater fertility and longevity of the survivors (due to lessened competition and relatively greater food

supply) soon brings the rat population back to its former level.

Rat trapping is best accomplished by dividing the locality into districts (each trapper being able to care for from 150 to 200 traps) which are grouped into zones and areas, surpervised by foremen and inspectors. In case the force is unable to cope with the whole area it is best to adopt some selective plan, such as that carried out by Heiser in Manila. Trapped rats are accurately tagged with place of capture, etc., and brought daily to headquarters, where they are rid of fleas by dipping in pure kerosene, and preserved on ice for laboratory study. Here all rats are nailed on shingles with magnetic hammers, organs and lymphnodes exposed by a median incision with lateral cuts on the limbs, and smears made from all suspicious rats. This is followed by rubbing suspected tissues on the abrased, shaved abdomen of a guinea pig. This should cause buboes and death within a week in positive cases. The typical lesions in the rat consist of (1) subcutaneous and visceral congestion; (2) buboes of inguinal, axillary and cervical lymphnodes (though these are common in rats from other causes); (3) focal necrosis of liver (granular or "peppery") or fatty degeneration; (4) watery, hemorrhagic pleural effusion. (5) "Resolving plague" may be accompanied by abscesses or linear scars in the spleen. Confusion may be caused by rat leprosy, nematode infection, pseudotuberculosis and hemorrhagic septicemia of guinea pigs. In suspected human cases blood cultures of bipolar staining, Friedlander's bacilli have caused difficulties in diagnosis.

Fumigation is best obtained with hydrocyanic gas. This is performed in freight cars of

approximately 3,000 cubic feet as follows: With the door mostly shut and strips of paper pasted over it, a bucket containing two pints of commercial sulphuric acid and three pints of water is placed inside. Into this is dropped 18 ounces of sodium cyanide, and the door shut and sealed before the gas begins to arise. This is left for one hour, when both doors are opened and the car well ventilated before anyone is allowed to enter. Essentially the same procedure is adopted on shipboard (preferably empty of cargo), although it is not considered possible to kill all the rats with one fumigation as it is in freight cars, appropriate blowers and exhaust fans are used and white mice and cats in cages used to test subsequent ventilation. Cage traps are only used where it is necessary to get live animals for experimental work (inoculation, number of fleas, etc.) or when a female in heat is used to attract males. Barrel traps are only occasionally used. Important items in rat trapping are to get or teach experienced trappers and supervisors, confine each trapper strictly to his own district, and to place a bounty on the rats caught, live or dead.

(3) *Rat Survey.* This important measure ("the eyes of the campaign") may be conducted either when plague infection is suspected, is present or has recently been eradicated. The number of rats to be caught varies with local circumstances, but to be entirely adequate should be 10% of the human population. The cost is estimated to be between 50 cents and $1.30 per rat. If rats are caught and examined as above described, an accurate picture can be obtained of the number and distribution of the normal and infected rat population. It has always been the history of well-observed plague

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outbreaks that the epizootic has existed in increasing amounts in the rat population for several months before it has attacked mankind, and this has often become apparent through the observation of an unusual number of dead rats. Occasional surveys, therefore, in cities, either free from plague or where it has been recently eradicated, will give accurate reassurance of continued freedom in the near future. Without adequate surveys the epizootic may reach dan-

FIG. 2. Interior (with flooring removed) of site of first case of human plague. Beaumont. Preliminary to disinfection.

gerous proportions, as in the recent case of New Orleans, where human plague recrudesced after two years of freedom had given an unwarranted sense of safety.

(4) *Treatment of Cases.* Plague cases are best treated with serum from horses immunized with a variety of strains of B. Pestis. Immunization is accomplished by the usual subcutaneous and intravenous injection, and doses up to 200 cc. given at frequent intervals intravenously. These are usually preceded by morphine and atropine. Unit standardization of the

serum had not yet been accomplished. Vacci-
nation of exposed individuals with B. pestis
(killed in the usual way) is also employed, al-
though if exposure has been grave (e. g., a known
bite from a rat flea) serum prophylaxis is pre-
ferred. Good results follow the use of serum
in the South to-day, although it is admitted that
the epidemic is not a virulent one. Other reme-
dial measures such as sedatives, cardiac stimu-
lation and anti-febrile measures are of course
employed as indicated.

(5) *Research Work.* There still remain
many important facts to be elicited about the
control of plague. For instance, (1) as to the
biology of the rat flea, little is known as to its
viability after death of the host, how far it will
travel to seek a human host, conditions govern-
ing such search, etc.; (2) importance of other
transmitters (such as bedbugs, lice, ants) and
of intermediate hosts other than the rat; (3)
conditions governing spread of infection by
land routes (4) and types of disease (bubonic,
pneumonic, or "pestis minor"); (5) impor-
tance of substrains of B. pestis as to violence of
epidemic; (6) production of vaccines; (7) pro-
duction of immune serum of higher titre and
standardized strength.

As regards the present plague problem in the
State of Pennsylvania and other northern states,
it would seem best to concentrate efforts on
"rat-proofing," so that when plague does appear
in this locality we shall be insured against its
rapid extension. Combined with this, there
should be occasional rat surveys in our single
large seaport. In view of the present state of
the country perhaps the greatest step would be
to secure state or local ordinances that all fu-
ture building-construction should be "rat-proof"

in the present sense of the term. A regulation that all repairs amounting to more than 50% of the total cost should necessitate rat-proofing the structure would also be of great value. It is of course obvious that even such measures would cost considerable private expense if vigorously enforced throughout the state, and that it would be many years before their full effect would be manifest. Nevertheless, as an insurance against plague, the expense would be justified many fold and if the economic gain can also be properly demonstrated it is not unreasonable to expect a certain amount of public coöperation. It

Fig. 3. Lodging House in Beaumont, the site of a case of human plague. Rat proofed with concrete and elevation. (See lower right hand corner.)

must be recognized, however, that as long as the public lacks the stimulus of the actual presence of plague, it will take energetic action on the part of health authorities and doctors to make the people alive to the situation. I am happy to say that a formal request has been made by the State Department of Health to the commission that is now revising the building laws, that ade-

quate provision for rat-proofing all future structures be inserted.

Any funds available through the present interest in the plague problem or for other reasons, should best be spent in assuring the efficient execution of the measures just described or in publicity measures, which would educate property holders and merchants as to the economic losses and sanitary dangers of a rat infested community. This would be carried out in the hope that eventually individuals would to a certain extent undertake rat-proofing and rat control at their own expense. "Deratization," being only of temporary value, should not be allowed to divert resources from permanent rat-proofing measures, as long as plague has not actually appeared in or near the community.

SUMMARY

1. The present pandemic of the plague, which has caused literally millions of deaths in the past 26 years, will be a constant threat to this country for at least another half century. The Manchurian pneumonic plague of 1911 has demonstrated the possibility of an extensive epidemic of the most virulent type, and transmitted over land, in a climate similar to our own.

2. Experience in this country for the past 15 years, and in the epidemic now existing in the Gulf States, confirms the generally held opinion that anti-plague measures should be directed chiefly against the rat.

3. In the prevention of plague, by far the most important measure is the process of "rat-proofing", accompanied by an occasional "rat survey."

4. In the actual presence of plague, both these measures should be accompanied by extensive

rodent extermination, together with isolation
and serum treatment of human cases.

5. Many plague problems still await solution
by special investigations.

6. In this state, until stimulated by the actual
presence of plague in the neighborhood, efforts
at rat-proofing had best be restricted to the in-
clusion in building laws of the adequate rat-
proofing of new structures or those undergoing
extensive repairs; and to publicity measures
which would educate property holders and mer-
chants as to the economic loses and sanitary dan-
gers of a rat infested community.

DISCUSSION

DR. M. HOWARD FUSSELL, Chairman (Philadelphia):
I should like to ask Dr. Krumbhaar if the pulmonary
form of plague can be disseminated by the sputum of
the patient suffering from the plague.

DR. KRUMBHAAR: Yes, unfortunately, it is chiefly
disseminated in this way by direct contact. The bu-
bonic form is disseminated by the bite of the flea.

CHAIRMAN FUSSELL: How about the serum?

DR. KRUMBHAAR: That has given very promising
results. There are apparently very many different
strains of the plague bacillus differing in cultural
characteristics. Serum was made in New Orleans by
taking twenty-six of the different strains secured on
different geographical sites; it was prepared in the
usual way by injecting at first very small doses, then
in larger and larger amounts. The serum is given to
the patient in as high as 200 c.c. doses, preceded by
morphine and atropine, and as soon as the patient
seems able to stand it the dose is repeated. It is
rather a heroic treatment, but the southern doctors
thought very highly of it. It is hard to estimate the
value of the serum. This has not been standardized
yet, and on top of that is the difficulty that the viru-
lence of the plague bacillus varies much. In Man-
churia one hundred per cent. died; not a recovery. In
other epidemics of the bubonic form, from seventy-
five per cent. down to as low as thirty per cent. die.
There is a form called "pestis minor" that is very un-

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important. It is hard to get an accurate estimation of the value of the serum; those who use it think well of it, but they are still trying to get a more potent and valuable serum.

DR. EDWARD MARTIN, Commissioner of Health (Philadelphia): Acting as your agent, and because it is obvious to any one who has given the least attention to this subject, and because the function of the Health Department is prevention, Dr. Krumbhaar was delegated to attend the Galveston convention, from which he has brought so many valuable suggestions.

As a result of this report, and in accordance with the attitude taken by the Health Department of the United States, there is now being incorporated in the new building code a clause in virtue of which every structure erected in Pennsylvania shall be rat proof. This adds only moderately to the expense, and it gives us the assurance of protection. It is acknowledged by all who have struggled against these epidemics in their large proportion, that rat extermination is impossible. It behooves Pennsylvania to act now, lest it have to spend not only millions but billions in a costly struggle against this destructive and fatal disease.

THE WASSERMANN REACTION IN NON-LUETIC CASES.

By T. McKean Downs, M.D.,

PHILADELPHIA.

(From the Undergraduate Medical Association, Medical School, University of Pennsylvania, and the Laboratories, Philadelphia General Hospital.)

On December 14, 1920, a young man, aged nineteen years, entered the medical wards of the Pennsylvania Hospital, service of Dr. George W. Norris, suffering from malaria, which he had contracted five months before on the coast of Mexico, while serving in the navy. He had been treated and supposedly cured, and was now suffering from a return of typical symptoms of tertian malaria. His previous medical history was negative. Up until five months previous he had never been ill enough to see a doctor, and he denied venereal history—never any sore on the genitals, no rash, sore-throat, falling of the hair, severe headaches or pains in his bones at any time. His family history was also entirely negative, father and mother living and well, and he never had heard that his mother had had miscarriages.

His physical examination was negative, except for the enlarged spleen characteristic of malaria, a slightly enlarged liver, and a marked pallor. His eyes and teeth were perfectly normal; there were but few palpable lymph nodes; supracondylar glands not felt; no periosteal nodes or bowing of the tibiæ; lungs clear; heart normal and genitalia negative.

His blood on admission showed red blood cells, 2,560,000; hemoglobin, 42 per cent, and was loaded with tertian parasites. Urine negative.

He was immediately put upon quinine, 30 gr. per day, and Blaud's pills, and at once began to improve.

On December 17, the laboratory reported that the patient's blood Wassermann was weakly positive. Spinal fluid was not examined. On December 21, the patient was discharged, with instructions to take quinine for ninety days, according to Bass's advice[1] and then return to have his Wassermann repeated.

[1] Bass, C. C.: Jour. Oklahoma Medical Association, 1920, 13, 281.

This case caused much discussion as to the significance to be attached to his positive Wassermann. There was an impression among the staff that malaria is frequently associated with a positive reaction, but as no one was definitely sure of this the decision was reached to ignore the Wassermann and treat his malaria, taking up the question of syphilis later. I may say here that he has not appeared since and has been lost track of. Letters to his address are returned by the post-office.

The question thus raised was only partially settled by reference to certain widely used text-books. Osler's *Practice*, edition of 1920, failed to mention the possibility that the Wassermann might be positive in diseases other than syphilis. Schamberg, in his *Dermatology*, edition of 1915, says only "Positive Wassermann reactions may be obtained in yaws, and in a proportion of cases of malaria, leprosy, etc., and within a period of twenty-four to forty-eight hours after the administration of ether."

Osler and Churchman (*Modern Medicine*, 1914) say the reaction is positive in syphilis, tubercular leprosy and fresh malaria; that in other fevers and wasting diseases partial deviation of complement may occur, but these reactions are not truly positive.

Lespinasse[2] says the reaction is not absolutely specific but is considered evidence of syphilis except in yaws, tubercular leprosy, some cases of relapsing fever, malaria during the febrile stage, some cases of experimental trypanosomiasis and beriberi. In all other cases it is impossible to rule out associated syphilis.

Connor[3] says that false positives are known to occur in leprosy, yaws, relapsing fever, malaria during the febrile stage and in diabetes with acidosis.

When the Wassermann reaction was first introduced it was supposed to be specific—to be dependent upon a specific substance in the blood. Subsequent investigation has shown this belief to be fallacious; but though the theory of the test has been impugned, investigation has merely confirmed the belief in its specificity. Its efficiency is very high—all early luetic cases can be detected if several tests are done at short intervals, provided the technic is right. At the same time there have been many reports of cases other than syphilis with a positive reaction. Many of these reports can be accounted for by faulty technic. The test is so complicated, and such meticulous accuracy is required in all its details, that there is a large leeway for error and the human equation. By now the test as done in a good laboratory can be relied on and the results of different men on the same specimen of blood are in most cases consistent, but this degree of efficiency did not always obtain.

[2] Tice's Practice of Medicine, 1920.
[3] Oxford Loose-leaf Medicine, 1921.

There is at present no standardized method generally accepted for conducting the test, and there are nearly as many modifications as there are workers in this field. The wonder therefore is that the test is so very reliable.

The antigens in most common use are the syphilitic, the Noguchi and the cholesterinized—the latter the most sensitive.

The reading of the test is important. The readings usually reported are four-plus, complete inhibition; three-plus, over 75 per cent inhibition; two-plus, 50-75 per cent inhibition; plus, 25-50 per cent; plus-minus, under 25 per cent; and negative, complete hemolysis. In many cases only four instead of five positive degrees are reported.

These five or six reports may, for all practical purposes, be condensed into three—positive, complete inhibition of hemolysis; negative, complete hemolysis; and doubtful, anything between the two. A positive reaction means syphilis if the few other conditions that are still recognized as giving a positive can be excluded. One single negative standing alone is worthless in excluding lues, but is very valuable confirmatory evidence, and a doubtful reaction must be interpreted by the clinician. It is unjust to any patient to diagnose syphilis by the *Wassermann alone,* unless it shows complete or practically complete hemolysis. In a case known to be luetic, a doubtful (one, two or three plus) reaction is an indication for further treatment.[4]

It is the clinician's business to interpret the test; the laboratory should merely report the behavior of the serum when tested. For this reason Craig thinks it better that the laboratory man should not know the history of the case, lest his reading of the test be biassed and erroneous.

There is hardly a disease known in which the Wassermann has not at some time been reported positive, but most often in the other protozoan diseases. So striking used to be the proportion of positives in these cases, that R. Müller, of Vienna,[5] decided that scarlatina could not be a protozoan disease because he so rarely found the Wassermann positive, though he says positives do occur, rarely, in the disease. (I need not say that Müller stands practically alone in this view of the reasons for regarding scarlet fever as non-protozoal in etiology.)

Müller found that in 88 per cent of cases of yaws the Wassermann reaction is positive. He records that the results of different authors in malaria are variable. Bohn, he says, found a positive reaction in 35 per cent of his 46 cases, the reaction disappearing when the malaria was cured.

Bauermann and Wetter (quoted by Müller) using larger mate-

4 See "The Wassermann Test," by C. F. Craig, 1921.
5 Die Sero-Diagnose der Syphilis, 1913, Vienna.

rial, found only occasionally an incomplete reaction, almost exclusively as the fever was rising. A reaction still positive three days after the disappearance of all fever, in their opinion, signifies lues.

Other non-specific positives are rare. The reasons why they do occur are not known. Müller gives 3 per cent positive in advanced tuberculosis and says that the test is very occasionally positive in various tumors, especially carcinoma, but only when the patient is *in extremis*, with generalized metastases.

Tubercular leprosy shows the large proportion of 19 per cent of positive reactions, but curiously enough, in Müller's experience, the anesthetic form was invariably negative.

Kolmer and Casselman[6] found the Wassermann to be weakly positive in 19 per cent of cases of psoriasis. Of 250 cases of scarlet fever they found none with a positive reaction.

They record 5 cases of malaria; 3 of these had negative reactions; of the other 2, 1 was frankly luetic. The history of the other patient was not obtained. In discussing this paper, Dr. John A. Roddy, of Philadelphia, said that in the Canal Zone, during the summer of 1913, he saw hundreds of cases of malaria on whose serum a Wassermann reaction was performed, with uniformly negative results.

Kolmer[7] says the reaction is highly specific, but is so beset with technical difficulties that much confusion has been caused. Many of the non-specific reactions that have been reported we now know must have been due to technical errors, though false positives undoubtedly occur. Usually there is no difficulty in differential diagnosis. Kolmer finds the reaction often positive in yaws and in leprosy. Positives have been reported in malaria during the febrile stage, but all of his 11 cases were negative. In scarlet fever the reaction is uniformly negative, though the opinion still prevails that the reverse is true.

Anesthesia and pellagra both are occasionally found associated with positive reactions.

The cerebrospinal fluid is much less subject to error than the blood serum. He has found it positive only in cases of yaws and of leprosy in addition to syphilis.

Baermann and Wetter[8] found no positive reaction in 10 cases of malaria.

Michaelis and Lesser[9] found 1 positive reaction in a large series of malaria cases.

[6] Penna. Med. Jour., 1913, **17**, 217.
[7] Text-book of Infection, Immunity and Specific Therapy, 1915, p. 465 et seq.
[8] Wien. klin. Wchnschr., 1908, **21**, 1765.
[9] Berl. klin. Wchnschr., 1908, **45**, 301.

Rudolph Buhman[10] found 5 positives in 99 miscellaneous non-luetic cases; 3 of these cases were tuberculous leprosy, the other 2 were tubercular, and later gave a fairly definite history of lues. Included in the list were 15 cases of scarlet fever and 10 of malaria, in all of whom the reaction was negative.

Craig[11] finds false positives with regularity only in yaws, tuberculous leprosy, some cases of relapsing fever, some malarial infections in the febrile stage only, and in some cases of experimental trypanosomiasis in animals. He says that tuberculosis is more commonly associated with syphilis than any other disease and that syphilis of the lung is not infrequently called tuberculosis. If syphilis be excluded, tuberculosis does not give a positive reaction. If the positive Wassermann in malaria persists after the disappearance of all fever, syphilis is a complication in the opinion of Craig and other observers.

Anesthetic leprosy is never positive; even in the nodular form it is difficult to be dogmatic, for this disease occurs almost exclusively among savage or uncivilized races, which are so thoroughly permeated with syphilis that to exclude it is very difficult in any given case.

A large percentage of positives in non-luetic conditions, in Craig's opinion, means faulty technic in the laboratory.

In 2643 non-luetic cases on whom the test was performed by this observer,[12] only 11 positives were found, 0.4 per cent. Four of these cases had malaria and the reaction disappeared with the fever. The other cases were divided as follows: tuberculosis 3; pityriasis rosea, 3; diagnosis not made, 1. Two of the tuberculous patients later gave suspicious histories and cleared up under anti-specific treatment.

M. O. Biggs,[13] reports 10 cases of "thyroidogenous psychosis," with varied mental symptoms and the ordinary symptoms of Graves's disease. In no case was there any evidence of lues either on physical examination or in the personal or family history. In every case the blood Wassermann was more or less strongly positive. None of these patients were operated upon nor was spinal fluid Wassermann done.

He reports 1 more case, not insane, a woman with Graves's disease of rather severe degree, of twenty-five years' standing. Her history and physical examination were entirely negative; Wassermann was positive at the time of operation. The operation was entirely successful. One year later the patient was symptom-free and her Wassermann was negative. No antiluetic treatment had been taken.

10 Tr. Am. Gyn. Soc., 1916, 41, 319.   11 Loc. cit.
12 Craig, C. F.: Am. Jour. Med. Sc., 1915, 149, 41.
13 Jour. Missouri Medical Association, 1919, 16, 326.

Jean Golay[14] gives the results of his experience in the following table:

Diagnosis.	No. of Specimens.	Negative.	Positive.
Health	13	13	
Scarlatina	19	18	1 weakly positive
Tuberculosis	13	12	1 weakly positive
Neoplasms	9	9	
Diabetes	1	1	
Pneumonia	2	2	
Icterus	3	1	2 weakly positive

A. Touraine[15] says that the reaction is usually positive in spirochetal and trypanosomal diseases. In chronic malaria he finds it always negative. In the acute form he very often finds it positive during the rise of the fever (202 cases out of 326) subsequently becoming negative.

He considers the reaction to be not infrequently positive in acute fevers in general, disappearing with the fever. In chronic infections —tuberculosis and leprosy—it is much less frequent. He says the reaction is often positive after anesthesia with ether and especially with chloroform, but never after nitrous oxide.

In the Hospital of the University of Pennsylvania, between 1906 (when the Wassermann reaction was first reported) and February, 1921, 75 cases of malaria occurred, but not until 1916 was a Wassermann done routinely on all cases. The earlier tests were done only where the history was suspicious or the diagnosis for a time in doubt. Twenty-one tests in all were done on malaria patients, but only 8 of these were routine.

Of these 21 cases the Wassermann was negative in 12, of which 3 were routine. In 6 cases the reaction was positive, in the presence of either a frank venereal history, or one strongly suspicious, *e. g.*, admission of gonorrhea, multiple miscarriages in wife, generalized adenopathy, etc. One case had a doubtful reaction with negative history; 1 other with suspicious history had anticomplementary serum and the test was not interpreted. This patient, however, was considered luetic at the time and a later Wassermann was positive outside. In only 1 case of the 21 tested was there a completely negative luetic history, with a weakly positive reaction. Concerning this patient, a young colored girl, Dr. George V. Janvier, of Lansdowne, Pa., her physician, reports that he has not seen her since she entered the hospital, and he knows nothing of her subsequent history.

In no case was the reaction repeated in the hospital, even in the probably syphilitic cases, nor is there any record of the time in the malarial cycle when blood was drawn for the test. It would be very interesting and important to know this in the 2 cases with

[14] Internat. Clinics, 1920, **4**, 79.
[15] Rev. de Méd., 1920, **37**, 103.

positive reactions and negative histories, but there is at present no way of finding this out.

In the Philadelphia General Hospital since 1910 there have been a total of 154 cases of malaria. Here, also, the Wassermann was not done as a routine measure but only in suspicious cases. In fact, 130 of the 154 cases were *not* tested. Of the remaining 24 the reaction was negative in 15, and 9 cases were either frankly luetic or lues could not be excluded. Here, also, the reaction was not repeated in the hospital and no record was made of the time in the malarial cycle when blood was drawn.

In the Pennsylvania Hospital from 1910 to the end of 1920 there have been 232 cases of malaria, of which only 27 were subjected to the Wassermann reaction. Of these 20 were negative, 6 were positive, but lues was not excluded. One case showed a false positive. This is the only case I have seen in which the time of drawing blood could be established and where the reaction was repeated with negative results.

Case—J. F., admitted to the Pennsylvania Hospital August 30, 1914, suffering with malaria: Venereal history negative--denied venereal and the physical examination was likewise negative. He had a chill August 30, the day of admission, and one the next day, but none thereafter. On September 1 his Wassermann was reported positive on blood that was therefore taken either during or very shortly after a chill. He was discharged very much improved on September 4, and his second Wassermann was reported negative on September 5, the next day. It seems likely that blood for this test was taken on September 4—or at any rate long enough after his last chill for the malaria to have ceased to influence his serum.

To summarize, 461 cases of malaria have been examined; 73 of these, or 16 per cent, were subjected to the Wassermann test. Of these 73, 23, or 32 per cent, were positive, with lues not satisfactorily excluded; 47, or 65 per cent, were negative, and 3, or 4 per cent, showed a positive reaction, when lues could definitely be ruled out, as far as history and physical examination will allow.

These figures are inconclusive, though as far as they go they are in accordance with those given by various authors quoted above, with the exception of Touraine, who found the elevated proportion of 202 positives out of 326 malaria patients tested. I cannot explain his results other than by assuming that he was not careful to exclude lues or that his laboratory was at fault. However, to speak definitely, we should have to know what the reaction was in those 389 cases I report who were not tested.

Tuberculosis. The last 500 cases of tuberculosis occurring in the Philadelphia General Hospital were studied. The great majority of these were severe and far advanced cases, for the

incipient cases rarely come to this hospital. Here, also, the great
majority of the cases were not tested—only 179 tests or a little
over 35 per cent; the reaction was more often done here when the
physical examination and history were negative than in the malaria
cases.

Of the 179 cases in which the reaction was tested, 38, or 20 per
cent, were either frankly luetic or lues was not excluded to my
satisfaction; 135, or 76 per cent, were negative, and 6, or 45 per
cent, had a reaction more or less strongly positive, in the presence
of a negative history and physical examination.   I append abstract
histories of these 6 cases:

1. W. E., severely ill with pulmonary tuberculosis. History
and physical examination negative for lues. Sputum positive for
tuberculosis.
  Wassermann: Cholesterinized antigen, double plus; Noguchi
antigen, plus; luetic antigen, plus.
  No antiluetic treatment; later all antigens negative.
  Patient died of tuberculosis June 23, 1920. No autopsy.

2. J. C., admitted with advanced pulmonary tuberculosis.
History and physical examination negative for lues. Sputum
positive for tuberculosis.
  Wassermann: Cholesterinized antigen, plus; Noguchi antigen,
negative; luetic antigen, negative.
  Not repeated.
  Died August 9, 1920.   No autopsy.

3. F. P., admitted with advanced pulmonary tuberculosis.
History and physical examination negative for lues. Sputum
positive for tuberculosis.
  Wassermann: Cholesterinized antigen, plus; Noguchi antigen,
negative; luetic antigen, negative.
  Subsequently repeated with same result.
  Died August 29, 1920. No autopsy.

4. A. S., admitted with advanced tuberculosis. History and
physical examination negative for lues. Sputum positive for
tuberculosis.
  Wassermann: Cholesterinized antigen, plus; Noguchi antigen,
negative; luetic antigen, negative.
  Not repeated.
  Died September 18, 1920. No autopsy.

5. Anna S., admitted with advanced pulmonary tuberculosis.
History and physical examination negative for lues. Sputum
positive for tuberculosis.

Wassermann: Cholesterinized antigen, double plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died September 17, 1920. No autopsy.

6. C. H., admitted with acute tuberculous pneumonia, gravely ill. History and physical examination negative for lues. Sputum filled with tubercle bacilli.

Wassermann: Cholesterinized antigen, double plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died December 18, 1920. Autopsy confirmed antemortem diagnosis, and showed many other tuberculous lesions as well, but no evidence of lues, either grossly or on microscopic examination.

It will be noted that in all these cases three antigens were employed. In 5 of these cases the cholesterinized antigen alone was positive; only once did the other antigens react positively also. Of course it is impossible to speak dogmatically from only 6 cases, but this seems to show a hypersensitiveness on the part of this antigen that would detract somewhat from its value in diagnosis. It was indeed remarkable in looking over the hospital records to see how often the cholesterinized antigen would be strongly positive while the other two were either weakly positive or negative.

Hyperthyroidism. A study of the cases of hyperthyroidism and exophthalmic goiter cases in the Philadelphia General Hospital and University Hospital was made, but it was found that the Wassermann was so seldom done on these cases in the Philadelphia Hospital and in the surgical wards of the University that nothing was revealed. The same was true of the medical wards of the University before 1915.

After 1915 there were a total of 90 cases of Graves's disease and hyperthyroidism in the medical wards of the University. Of these, 1 (1.1 per cent) had frank lues and 38 (42.2 per cent) were not tested. The remaining 51 (56.6 per cent) cases had negative Wassermanns. A total of 13 tests were also done in the surgical wards and at the Philadelphia General Hospital, and these 13 were also negative. In only 1 case of 103 examined was a positive Wassermann found, and that patient had definite lues.

This is contrary to the statement of Biggs above, but I believe is in line with the experience of others.

Drs. D. J. McCarthy, C. H. Frazier and George W. Norris, all of Philadelphia, inform me that in their very extensive experiences with hyperthyroidism they have not met with any cases associated with a positive Wassermann.

It is proverbially impossible to prove a negative, but in Phila-

delphia at least the proportion of positive Wassermanns in hyper-
thyroid cases seems to be much less than in the general run of un-
selected hospital admissions.   The small number of cases I present
shows no evidence that hyperthyroidism stands in any causal
relation to the Wassermann reaction.

MALARIA.

Wassermann positive and lues excluded.	Wassermann negative.	Wassermann positive and lues not excluded.	Wassermann not done.
3	47	23	388

TUBERCULOSIS.

6	135	38	321

EXOPHTHALMIC GOITER.

0	64	1	108
Totals 9	246	62	817

Conclusions.   1. The Wassermann reaction is invariably positive
at some time during the course of syphilis, if properly performed,
and at sufficiently frequent intervals.

2. It is but rarely positive in non-luetic diseases.

3. It is unusual for it to be positive in malaria. If positive,
it is only weakly so (doubtful in Craig's classification) while the
fever is rising, becoming negative between paroxysms.

4. It is rarely positive in tuberculosis, and when positive the
reaction is weak or doubtful (*i. e.*, not diagnostic of lues in the
absence of history or signs).   I have found it positive only in
far-advanced cases shortly before death.

5. It is not positive in uncomplicated hyperthyroidism.

6. The cholesterinized antigen is probably too delicate to be
of value alone in diagnosing lues when there is no history or physical
evidence of disease.   It is invaluable in following the course of
known syphilis under treatment, by reason of its delicacy.

I desire to express here my deep gratitude to Dr. Edward B.
Krumbhaar, director of laboratories, Philadelphia General Hospital,
for his unfailing kindness and great courtesy to a beginner in
medicine.

STUDIES IN HEMOLYTIC STAPHYLOCOCCI

HEMOLYTIC ACTIVITY—BIOCHEMICAL REACTIONS— SEROLOGIC REACTIONS

A Thesis Submitted to the Graduate School of the University of Pennsylvania in Partial Requirement for the Degree for the Doctor of Philosophy.

LOUIS A. JULIANELLE

STUDIES OF HEMOLYTIC STAPHYLOCOCCI

HEMOLYTIC ACTIVITY—BIOCHEMICAL REACTIONS—SEROLOGIC REACTIONS

Louis A. Julianelle

From the Bacteriological Laboratories of the School of Hygiene, University of Pennsylvania and the Philadelphia General Hospital, Philadelphia

I. STUDY OF HEMOLYTIC ACTIVITY

That staphylococci lake blood was brought out in 1900, when Kraus [1] noticed the hemolytic effect of staphylococci on bloodplates. The following year Neisser and Wechsberg [2] demonstrated a hemolytic substance in filtrates of broth cultures. They found that in alkaline beef broth, this hemolytic substance began to appear on the fourth day and reached a maximum between the eighth and fourteenth day. In a general way they showed that aureus and virulent strains produced greater quantities of hemolysins than did either the albus or avirulent strains. Van durme [3] found that the hemolytic power was generally greatest in cultures freshly isolated from pathologic conditions, and was generally absent in cultures from dust and from the normal mouth. Todd,[4] working with B. megatherium and Kraus [5] working with staphylococcus showed that this action takes place in vivo as well as in vitro.

PRODUCTION OF HEMOLYSIN

It had been observed that in a general way staphylococci would show hemolysis to a greater or less extent on blood-agar plates within 24 hours. In addition, the hemolysis was not typical of an exogenous hemolysin, as is typical of Streptococcus hemolyticus; but rather resembled an exogenous product of metabolism, as in the case of B. coli, where the hemolysis diffuses haphazardly through the medium.

The first experiment was made to determine what analogy there was in chronicity in the production of hemolysins on blood plates and in broth. It might be stated here that all the work on hemolytic activity was obtained with 4 cultures representative of all the strains studied. Two were known hemolytic, and 2 were originally isolated as nonhemolytic. Twenty-four hour cultures were seeded into 10% horse (inactivated) serum broth in Erlenmeyer flasks and incubated at 37 C. for 24 hours. At the end of each 24-hour period, 5 c c of the culture were removed

1 Wien. Klin. Wchnschr., 1900, 13, p. 49.
2 Ztschr. f. Hyg. u. Infektionskr., 1901, 36, p. 299.
3 Hyg. Rundschau, 1903, 13, p. 66.
4 Trans. London Path. Soc., 1902, 53, p. 196.
5 Wien. klin. Wchnschr., 1902, 15, p. 382.

aseptically and centrifuged at high speed for 5 minutes. One c c of the clear supernatant fluid was added to 1 c c of a washed 2.5% horse-blood suspension and incubated at 37 C. for 2 hours, at the end of which time the tubes were read for hemolysis. The concentration of blood attempted to approximate as closely as possible the conditions of the blood plate.

It was found that no estimable hemolysins were produced in broth cultures within 24 hours. In fact, as will be borne out later, no hemolysins were shown to be present until the sixth day. It may be that the discrepancy in time between plate and broth cultures is explainable on the grounds that in the former case the hemolysins are so concentrated around each colony as to assert themselves at a conspicuously earlier period; whereas in the latter case the hemolysins go into solution and become too dilute to have any effect on a suspension of blood cells.

The next experiment was planned to obtain the curve for the production of hemolysins. The technic employed was the same as in the preceding experiment, except for one detail. The cultures were seeded into tubes containing 10 c c of the serum broth, and at the end of each day one tube was removed from the incubator and used for the tests. Care was taken to keep the volume of the tubes constant by adding sterile salt solution to repair any loss by evaporation.

Table 1 shows that hemolysins begin to appear on the sixth day, reach a maximum at the ninth and tenth days, and disappear between the thirteenth and sixteenth days.

With the period of hemolysin production established, the logical sequence was to determine if possible the source or the cause of the production. It was assumed entirely theoretically that hemolysis is caused by one of the following or perhaps combination of factors:

1. Reaction: An increase or decrease in hydrogen-ion concentration sufficient to cause hemolysis.

2. Tonicity: An increase or decrease in the tonicity of the medium sufficient to cause crenation or laking of the blood corpuscles.

3. Hemotoxin: A hemolytic substance elaborated and secreted by the bacterial cell, causing hemolysis.

4. Proteolysis: The production by the bacterial cell of some substance for the utilization of the blood protein. Under this head would be included autolytic products also.

In order to establish experimentally which hypothesis was correct the following procedure was adopted: Coincidental with testing for the

presence of hemolysins, the hydrogen-ion concentration was read on the Clark and Lubs [6] scale; the amino acidity was titrated by the Sörensen [7] method; the proteose content was determined by the Vernon tests; [8] and numerical counts made at the end of each day, as long as was deemed necessary for the points at hand.

TABLE 1
PRODUCTION OF HEMOLYSINS

	Days															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Strain A1 (From Air)																
Hemolysis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amino acidity	54	56	56	56	56	54	58	58	50	50	50	50	4.6	38	36	36
Proteose content	0.25	0.25	0.25	0.25	0.25	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
H-ion concentration	7.9	7.9	8.0	8.1	8.2	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.4	8.4	8.4	8.4
Strain A5 (From Air)																
Hemolysis	0	0	0	0	0	0	±	+	+++	++	+1	+	+	+	±	0
Amino acidity	56	64	64	56	84	80	98	102	88	84	84	84	72	72	44	44
Proteose content	0.25	0.25	0.25	0.25	0.3	0.3	0.35	0.4	0.4	0.4	0.4	0.45	0.45	0.45	0.45	0.45
H-ion concentration	7.7	7.9	8.0	8.0	8.2	8.3	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4
Strain H2 (From Heart Blood)																
Hemolysis	0	0	0	-0	0	0	0	0	0	0	0	0	0	0	0	0
Amino acidity	54	56	56	56	56	56	54	52	46	44	44	44	38	36	34	34
Proteose content	0.25	0.25	0.25	0.25	0.25	0.3	0.3	0.3	0.25	0.3	0.3	0.3	0.3	0.3	0.3	0.3
H-ion concentration	7.7	7.9	8.0	8.2	8.2	8.2	8.2	8 2.	8.2	8.3	8.3	8.3	8.4	8.4	8.4	8.4
Strain T9 (From Throat)																
Hemolysis	0	0	0	0	0	0	±	+	++	+	+	+	±	0	0	0
Amino acidity	54	56	56	56	56	54	86	74	66	56	56	56	58	44	38	38
Proteose content	0.25	0.25	0.25	0.25	0.25	0.3	0.3	0.3	0.3	0.3	0.3	0.35	0.35	0.35	0.35	0.35
H-ion concentration	7.7	7.9	8.0	8.1	8.2	8.2	8.2	8.2	8.3	8.3	8.3	8.3	8.4	8.4	8.4	8.4

	Hemolyis	Amino Acidity	Proteose	H-ion
Control	0	38	0.25	7.5

Figures for proteose content represents amount of medium required to equal 1 c c of standard.

Figures for amino-acidity represent c c of 20/N NaOH required to neutralize 100 c c of medium.

Plus signs indicate: +, 25% hemolysis; ++, 50%; +++, 75%.

Hours	Bacterial Counts Made With Production of Hemolysin Stains			
	A 1	A 5	H 2	T 9
0	40,000	72,000	50,000	73,000
24	100,000,000	180,000,000	450,000,000	300,000,000
48	830,000,000	990,000,000	850,000,000	1,000,000,000
72	1,210,000,000	6,300,000,000	8,900,000,000	9,200,000,000
96	7,600,000,000	1,000,000,000	2,500,000,000	2,000,000,000
120	460,000,000	300,000,000	3,200,000 000	800,000,000
144	150,000,000	350,000,000	800,000,000	600,000,000

1. An analysis of the results (table 1 and chart 1) shows several points: The ultimate reaction of all the cultures—hemolytic and non-

[6] Jour. Bacteriol., 1917, 2, p. 109.
[7] Biochem. Ztschr., 1908, 7, p. 45.
[8] Jour. Physiol., 1904, 30, p. 330.

hemolytic alike—is the same, P_H 8.4. If the hemolysis were the effect of reaction, all the cultures should show a like behavior on blood. But since the cultures do not show the same hemolytic activity, it is reasonable to exclude reaction as the cause of hemolysis. Incidentally, sterile salt solution, the reaction of which is .adjusted to P_H 8.4, does not cause hemolysis.

Charts 1 and 2.—Showing counts, amounts of amino acids and hemolytic substances produced.
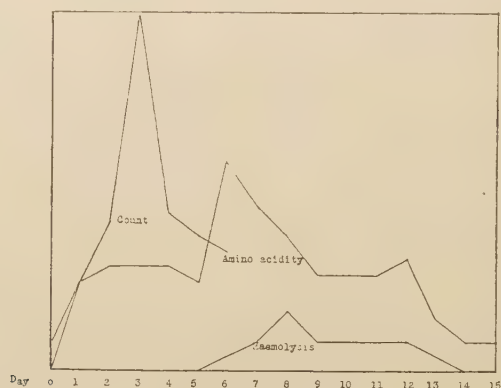
Fig. 1.—Strain T9.
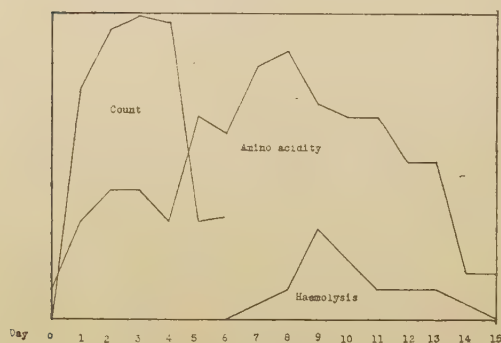
Fig. 2.—Strain A5.

2. No effort was made to determine the tonicity of the cultures. The impression was gathered from the work of Larson et al.[9] that bacteria of themselves do not change the surface tension of mediums, and in their study specific depressants were added when a drop in surface tension was desired.

[9] Larson, Cantwell, and Hartzell: Jour. Infect. Dis.. 1919. 25, p. 41.

3. The figures for the numerical counts show that there is an increase in the number of staphylococci until the third day, when a maximum is reached. From then on there is a sharp decrease in numbers, indicating that growth of an active nature at least has come to a cessation. If the production of hemolysins and the numerical counts had shown a parallelism, it could have been reasonably assumed that the hemolysin were a true secretion product and a definite hemotoxin. Since they show no such parallelism, however, the hemolysin must be of some other nature.

4. The course of proteolysis or amine acidity runs a definitely parallel course to the curve of hemolysin production. The suggestion offered itself that if not directly associated, then some close relationship must exist between the two. Further study reveals the following concatenation of events: (1) the period of maximum growth occurs on the third and fourth day; (2) the maximum production of amino acidity occurs on the seventh and eighth days; (3) the maximum production of hemolysins occurs on the ninth and tenth days. Stated in another way, the growth period precedes the amino acidity period, which in turn precedes the hemolysin production period. It would seem from such an interrelated process that the production of hemolysins is a proteolytic process and perhaps even autolytic.

There is one other point of interest brought out by this experiment. Although there is an increase in amino acidity, there is no corresponding decrease in proteose content. This is probably due to the fact that the biuret test, used in determining the amount of proteose present, shows the presence of substances other than proteose; so that even if proteose were proteolyzed to form polypeptides, peptides and the higher amino acids the intensity of the color would still remain the same. One other point—it shows that the production of erepsin by staphylococci enables them to attack peptones and proteoses.

5. Following the suggestion offered in the foregoing experiment, the next step was to determine what rôle autolysis plays in hemolysis. For this purpose 24-hour cultures were inoculated in Erlenmeyer flasks (10% serum broth), and incubated at 37 C. for 5 days. This culture was then distributed in equal volumes into test tubes. To one series was added 0.25% phenol, to a second 10% HCC13; a third series was incubated at 45 C.; and a fourth was left untreated and incubated with the first and second series at 37 C. The object of this procedure was to determine whether after the maximum growth period was reached

and the cultures were inactivated by chemical or heat, with the enzymes still capable of activity, hemolytic substances were being produced. Each day tests were made for the presence of hemolysins. After the first day, guinea-pig serum and a living (24-hour) culture in 1 c c quantities were added to the 45 C. specimen. This was to supply complement, if it were needed, and any other vital substances necessary for hemolysis that a growing culture might possess. The results are appended in table 2, which shows: 1. No hemolysin was formed in cultures subjected to antiseptics or heat. 2. Complement does not appear necessary for hemolysis. 3. A living culture produces hemolysis per se, and is

TABLE 2

SHOWING EFFECT OF HEAT AND CHEMICAL AGENTS ON PRODUCTION OF HEMOLYTIC SUBSTANCE

	Days									
	1	2	3	4	5	6	7	8	9	10
Strain A5 (From Air)										
Phenol....................	−	−	−	−	−	−	−	−	−	−
HCCl₃.....................	−	−	−	−	−	−	−	−	−	−
45 C.	−	−	−	−	−	−	−	−	−	−
45 C. + complement..........	*	−	−	−	−	−	−	−	−	−
45 C. + 24 hour culture........	*	±	−	+	+	+	+	+	*	*
Untreated...................	+	+	+	+	+	+	+	±	−	−
Phenol....................	−	−	−	−	−	−	−	−	−	−
HCCl₃.....................	−	−	−	−	−	−	−	−	−	−
45 C.	−	−	−	−	−	−	−	−	−	−
45 C. + complement..........	*	+	−	−	−	−	−	−	−	−
45 C. + 24 hour culture........	*	+	+	+	+	+	+	+	*	*
Untreated...................	+	+	+	+	+	+	+	±	−	−
Phenol....................	−	−	−	−	−	−	−	−	−	−
HCCl₃.....................	−	−	−	−	−	−	−	−	−	−
Complement..................	*	−	−	−	−	−	−	−	−	−
Strain A5....................	*	+	+	+	+	+	+	+	*	*
Strain T9....................	*	+	±	+	+	+	+	+	*	*
Salt........................	−	+	−	−	+	−	−	−	−	−

* = no test conducted. Day 1 is 1st day under treatment, but 6th day of age of culture.

consequently worthless in such an examination. These results do not show that hemolysin is of an autolytic nature; neither do they show that it is not of an autolytic nature. The conclusion to be drawn is that in the case of heat, the hemolysin being thermolabile, is possibly dissipated; while in the case of the antiseptics, the hemolysin is so closely associated with the bacterial cell that destruction of the latter means lack of manifesation from the former. This falls somewhat in line with the work of Gordon on meningococci, showing that hemolysins are endocellular and are liberated on autolysis of the bacterial cells.

Effect on Hemolytic Activity of Successive Transplantation in Blood-Free Medium.—The object of the next experiment was to

determine whether a hemolytic strain of staphylococcus is always hemolytic. No definite references to the loss of this haemolytic manifestation could be found in the literature. Transplants were made daily into peptone broth, and at the end of each week blood-agar plates were streaked to show whether the cultures were still hemolytic. After the second week, since the plates were readily hemolyzed, the cultures were transplanted every other day, and after the first month every week. The reason for this change of procedure was the assumption that by daily transplantations the cultures were kept very active and that it would be more difficult, if possible, to suppress so vital a quality.

This experiment was continued for more than four months, and at the time of writing the cultures were still hemolytic. On some occasions there appeared to be retardation in hemolysins, and then the following week the cultures were as actively hemolytic as originally. Since the retardation was neither progressive nor continuous, it is reasonable to assume that it was probably due to differences in the blood used for the work. Normal horse blood, which was used for the blood-agar plates in this experiment, has been shown by Neisser and Wechsberg [2] to possess small quantities of antihemolysin. This normal quantity, however, may have been sufficient to delay nemolysis. It would seem, therefore, that hemolytic cultures tend to remain hemolytic.

Effect on Nonhemolytic Strains of Successive Transplantations in Blood Medium.—In this case the point at hand was to determine whether nonhemolytic cultures could be made hemolytic by adaptation to blood medium. If nonhemolytic cultures can be made to lake blood, it may be said that any strain of staphylococcus is hemolytic, adding provisionally that continual adaptation to a blood-free habitat ultimately suppresses its hemolytic activity and keeps it in abeyance; but readaptation to a blood-containing medium will restore the suppressed activity. Table 3 shows that after a period of 7 months, certain strains regained their hemolytic ability. It may be that this power was recovered at an earlier period, but tests were not definitely made until the stated lapse of time.

It should be added here, in view of a wealth of work in a hospital laboratory, that we think every strain of staphylococcus is definitely hemolytic. The strains will vary in degree of hemolysis, and in rapidity of hemolysis, but if sufficient time is given, all strains will show hemolysis. When the strains under study were isolated, a period of 6 days was given to determine hemolysis on blood plates, and it is now apparent

that the 6 days were not sufficient. Other cultures not included in this survey did show hemolysis after the arbitrarily chosen time, and attempts to collect nonhemolytic strains after 10 and in rarer cases 12 days, have failed. So that it seems by virtue of this evidence that the strains we originally labeled nonhemolytic were in reality hemolytic, and that their hemolytic character was very much suppressed. It would seem, therefore, that it can be definitely stated that cultures which did not show hemolysis within 6 days were able to give definite signs of hemolysis on blood plates within 24 hours and complete hemolysis within 48 hours.

Since the completion of this experiment every strain of staphylococcus isolated (whether a contaminant or a pathogen) was held for study. The number of days required to show beginning hemolysis was recorded. These results are tabulated in table 4. It will be seen that every strain shows hemolysis, but that the factor of time plays an

TABLE 3

DEVELOPMENT OF HEMOLYSIS BY NONHEMOLYTIC ? STRAINS

	April, 1921	November, 1921		April, 1921	November, 1921
A 1	No hemolysis	Hemolysis	P 5	No hemolysis	Hemolysis
A 2	Hemolysis	Hemolysis	S 2	Hemolysis	Hemolysis
A 3	Hemolysis	Hemolysis	T 1	No hemolysis	Hemolysis
A 5	Hemolysis	Hemolysis	T 2	Hemolysis	Hemolysis
F 1	No hemolysis	Hemolysis	T 3	Hemolysis	Hemolysis
H 2	No hemolysis	Hemolysis	T 5	Hemolysis	Hemolysis
P 1	Hemolysis	Hemolysis	T 6	Hemolysis	Hemolysis
P 2	Hemolysis	Hemolysis	T 8	No hemolysis	Hemolysis
P 3	Hemolysis	Hemolysis	T 9	Hemolysis	Hemolysis
P 4	Hemolysis	Hemolysis	X	No hemolysis	Hemolysis

important part. Thus it is seen that in a general way aureus strains show hemolysis earlier, and that virulent strains also show hemolysis earlier than the saprophytic; but the point is clear that white and aureus strains, saprophytic and parasitic alike, become hemolytic. In the case of nipples, for example: These are supposedly sterilized and sent to the laboratory to be tested for sterility so that it is logical to assume that any growth is apt to be contamination. Yet the 9 white strains are as rapidly hemolytic as the 18 orange strains isolated from pus.

Effect of Carbohydrates on Hemolysis.—It has been shown by Ruediger,[10] Lyall,[11] Davis,[12] Sekiguchi,[13] Stevens and Koser[14] and

[10] Ibid., 1906, 3, p. 663.
[11] Jour. Med. Res., 1914, 30, p. 515.
[12] Davis: Jour. Infect. Dis., 1917, 21, p. 308.
[13] Ibid., 1917, 21, p. 475.
[14] Jour. Exper. Med., 1919, 30, p. 539.

others, that carbohydrates prevent hemolysis by streptococcus, and it was problematic just what their effect on staphylococcus hemolysis would be. Two experiments were carried out to determine this point. In the one case, cultures were planted into 10% serum broth plus 1% dextrose. After 9 days tests were made for hemolysis and H-ion concentration read—to assure ourselves that an acidity would not interfere with the test. The results were: for 10% serum broth, dextrose 1%, strain A5 gave P_H 6.4, hemolysis and strain T9, P_H 7.6 and hemolysis.

Incidentally both these strains were streaked on lactose-blood-agar plates, and in both cases hemolysis was produced within 24 hours. In the second case, cultures were planted into peptone broth plus 1% dextrose. The test for hemolysis was positive after 24 hours, but the

TABLE 4
HEMOLYTIC ACTIVITY OF CONSECUTIVE CULTURES

Source	Pigment	No. of Cultures	Average Time for Hemolysis
Air	White	8	6–7 days
	Yellow	2	1–2 days
Sputum	White	1	3 days
	Aureus	2	1 day
Skin	White	4	4 days
Throat	White	4	1 day
	Yellow	1	1 day
Tonsil	White	1	1 day
	Aureus	1	1 day
Nipple	White	9	1–2 days
	Aureus	2	1 day
	Yellow	2	1 day
Feces	White	2	3 days
	Yellow	1	2 days
Pus	Yellow	3	2 days
	Orange	18	1–2 days
Necropsy	Aureus	3	1–2 days
	Yellow	1	1 day
Water	White	2	4 days
Contamination (source unknown	White	3	7 days

hemolysis was not typical, showing a browning similar to acid hematin formation. Consequently the P_H value was determined and found to be 4.4. The reaction was adjusted to neutrality and hemolysis no longer took place. Approaching the question from another tangent, sterile salt solution adjusted to a reaction of P_H 4.4 caused the same type of hemolysis.

It would seem from these experiments that carbohydrates do not influence hemolysis as produced by staphylococcus. Regarding the acidity produced in the peptone broth and not in the serum broth, it is easily conceivable that the buffer qualities of the serum in the latter obscure the acid formed by fermentation of dextrose.

Effect of Heat on Hemolysis.—Neisser and Wechsberg [2] found that heating the staphylococcus "hemolysin" for 20 minutes at 56 C. would completely inactivate it.

In determining the effect of heat on the hemolytic action, the supernatant fluids of centrifuged 9-day cultures were heated at 56 C. for 30 minutes, and it was found that the hemolysin of staphylococcus is a thermolabile substance, which can be destroyed by heating in this way.

DISCUSSION

Previous investigators of the hemolytic activity of staphylococcus were concerned with observations of the hemolytic activity per se. Aside from some speculations as to its relation to pigment, virulence and agglutination, no attempt was made to arrive at its causation. The point under study here was concentrated on the cause of the hemolytic activity, and the period of its development was only a coincidental observation, since this phase of it was already sufficiently elaborated by previous investigators.

Our results point to a process of proteolysis—perhaps associated with autolysis—as the cause of hemolysis. This is not a new conception —it has been shown to be the fundamental of meningococcus hemolysis and were experiments performed to establish the point of possibly B. proteus, B. coli, etc. Although we have been unable to demonstrate irrevocably that autolysis is the specific cause, it is very significant that the period of maximum growth first appears, then the period of maximum amino acidity, and, finally, the period of maximum hemolysis. Such a sequence of evidence can point only to autolysis.

It must be for this reason that we have been unable to suppress the hemolytic activity of our hemolytic strains. If hemolysis is due to so important a function as protein-splitting, the factor involved is too vital to be eradicated by continued growth in blood-free mediums. Conversely, it is no wonder that slowly hemolytic cultures will increase in rapidity of hemolysis by continued adaptation to an environment where protein ultilization becomes more pronounced.

Nor is it phenomenal that sugar should not inhibit hemolysis in such a case. Kendall and Walker's [15] conception that the presence of glucose has a protein sparing effect and consequently retards production of proteolytic enzymes can be accepted only provided the hydrogen-ion concentration of the medium increases within suitable limits. For as

[15] Jour. Infect. Dis., 1915, 17, p. 442.

Berman and Rettger [16] pointed out, in tests in which buffers are employed proteolytic enzymes appear as soon in sugar mediums as in plain broth. And in serum broth, the buffer qualities of serum cannot be denied.

II. RELATIONSHIP OF HEMOLYTIC ACTIVITY TO OTHER METABOLIC ACTIVITIES

This part of the investigation concerns itself with a study of the biochemical reactions of the staphylococci, particularly as possible relations to hemolysis. Although, as the evidence submitted will show, hemolysis appears to be a separate entity from the biochemical reactions pursued, some new points of interest have been added to the literature of the hemolytic staphylococci.

CHROMOGENESIS

Except in a general way, a distinction of the chromogenic varieties of the staphylococci is an insignificant one. The pigment produced by bacteria is influenced to a greater or less extent by the medium employed for its production, and can be greatly modified by selection or by previous environment. Loeffler's serum medium, for example, without affecting the inherent power of chromogenesis always accentuates the depth of color produced by staphylococci. Pigment will vary with the amount of oxygen, the amount of moisture available, and the age of the culture.

So Neisser and Lipstein [17] offer the hypothesis that white cocci were originally orange cocci which have lost their chromogenic power. Rodet and Courmont [18] published the observation of the transformation of a white staphylococcus to an aureus and subsequently to a white again. Lubinski [19] showed that the orange forms lost their pigment when grown anaerobically; in some cases the recovery was delayed and in other cases the loss was permanent. Kolle and Otto [20] stated that chromogenic cocci lose their chromogenesis by heating to 85 C., by prolonged cultivation on artificial mediums, and by repeated animal passage. Winslow and Rogers [21] showed that a temperature of 50-55 C. may cause a loss in chromogenesis.

Neisser and Wechsberg showed that strains of both Staphylococcus albus and Staphylococcus aureus would produce hemolysins. This was later corroborated by both Kutscher and Konrich [22] and Koch. [23] Noguchi [24] and Rosen-

[16] Jour. Bact., 1918, 3, p. 389.
[17] Handbuch. d. pathog. Mikroorganismen, 1914, 3, p. 105.
[18] Compt. rend. Acad. d. sc., 1890, 9, p. 186.
[19] Centralbl. f. Bakteriol., 1894, 16, p. 769.
[20] Ztschr. f. Hyg. u. Infektionskr., 1902, 41, p. 369.
[21] Jour. Infect. Dis., 1906, 3, p. 485.
[22] Zetschr. f. Hyg. u. Infektionskr., 1904, 48, p. 249.
[23] Ibid., 1907, 58, p. 287.
[24] Arch. f. klin. Chir., 1911, 96, p. 696.

bach[25] show a relation between virulence and pigmented cocci, while Passet[26] and Fisher and Levy[27] show that the lightly colored or colorless forms are most often associated with disease processes.

EXPERIMENTS

In determining chromogenesis the technic employed was that suggested by Winslow and Winslow.[28] Cultures were grown on agar slants at 20 C. for 2 weeks. A portion of the growth was spread over white roughened paper, with a platinum loop and allowed to dry in air. The hue and tint were matched against the colors of the frontispiece of their book (table 5).

TABLE 5

SOURCES AND CHROMOGENESIS OF THE STRAINS STUDIED

A 1—From the air	Lemon yellow I
A 2—From the air	Medium cadmium yellow IV
A 3—From the air	Cadmium orange III
A 5—From the air	Medium cadmium yellow IV
F 1—From feces	White
H 2—From heart's blood at necropsy	Medium cadmium yellow V
P 1—From pus from spine	Cadmium orange IV
P 2—From pus from carbuncle	Lemon yellow I
P 3—From pus from acne	Cadmium orange IV
P 4—From pus from extracted tonsil	Cadmium orange IV
P 5—From pus (unclassified)	Cadmium orange IV
S 2—From skin	White
T 1—From throat	Orange yellow III
T 2—From throat	Medium cadmium yellow V
T 3—From throat	Medium cadmium yellow VI
T 5—From throat	Lemon yellow II
T 6—From throat	Lemon yellow III
T 8—From throat	White
T 9—From throat	Orange yellow V
X—From blood culture (case ferunculous)	Orange yellow III
C15—From throat	White
C16—From throat	White
C18—From throat	White
J 1—From pus	White
L 1—From pus	Cadmium orange IV

It will be seen at a glance that there is no relationship between pigment and hemolysis. The cultures are all hemolytic, and yet they vary from a white to a rich golden brown. This is scarcely surprising. The literature shows that pigment production may be varied, and while the hemolytic activity seems to be fixed, it could hardly be expected that the two functions would be related.

ACID PRODUCTION IN THE PEPTONE MEDIUM OF CLARK AND LUBS

Preparatory to the carbohydrate metabolism studies of staphylococci, this experiment was made to determine in a general way any relation-

[25] Dent. med. Wchnschr., 1884, 6, p. 31.
[26] Passet: Fortschr. d. Med., 1885, 33, p. 33.
[27] Dent. Ztschr. f. Chir., 1893, 36, p. 94.
[28] Systematic Relationships of the Coccocese, 1908.

ship between hemolysis and acid production. In view of the methyl red test of differentiation of B. coli and B. aerogenes by this medium, it seemed at the time that it might possess some value in this work. The peptone medium contained 0.5% K_2HPO_4, 0.5 peptone (Difco), and 0.5% dextrose, and was adjusted to P_H 7.4.

Table 6 shows the H-ion readings of the different cultures from time to time as specified. With the exception of A1, all strains reach an end-point of P_H 4.2-4.6 within 96 hours. Although there seem to be differences in the earlier readings, there is no line of demarcation between the acid production of the cultures. These differences are probably explainable on differences in numbers inoculated, periods of lag, etc.

TABLE 6

ACID PRODUCTION IN CLARK AND LUBS MEDIUM *

	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours	48 Hours	72 Hours	96 Hours
A 1	7.6	7.6	7.4	7.0	6.9	6.9	6.9	6.9
A 2	6.4	4.6	4.6	4.6	4.6	4.4	4.4	4.4
A 3	6.2	4.6	4.4	4.4	4.4	4.4	4.4	4.4
A 5	4.6	4.4	4.2	4.2	4.2	4.2	4.2	4.2
F 1	6.0	5.8	5.8	5.0	4.6	4.6	4.6	4.6
H 2	5.0	4.6	4.4	4.4	4.4	4.4	4.4	4.4
P 1	6.1	4.9	4.6	4.6	4.6	4.6	4.6	4.6
P 2	6.0	4.6	4.6	4.6	4.6	4.6	4.6	4.6
P 3	6.8	4.6	4.6	4.6	4.6	4.6	4.6	4.6
P 4	5.0	5.0	4.8	4.6	4.6	4.6	4.6	4.6
P 5	6.6	5.0	4.6	4.4	4.4	4.4	4.4	4.4
S 2	7.6	5.8	5.0	5.0	4.6	4.6	4.6	4.6
T 1	5.0	5.0	4.8	4.8	4.6	4.6	4.6	4.6
T 2	5.4	4.8	4.8	4.6	4.6	4.6	4.6	4.6
T 3	5.0	4.9	4.9	4.6	4.6	4.4	4.4	4.4
T 5	5.0	4.8	4.6	4.4	4.4	4.4	4.4	4.4
T 6	7.6	6.6	6.0	5.4	4.6	4.6	4.6	4.6
T 8	5.5	5.0	5.0	4.8	4.8	4.8	4.6	4.6
T 9	7.4	5.6	5.0	5.0	4.6	4.6	4.6	4.6
X	6.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Control	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2

* Figures represent values of H-ion concentration.

At this point, the question arose as to what determined the acid end-point of the cultures. To approach an answer, 2 experiments were planned: (1) Cultures were grown in the same medium with the reaction adjusted to P_H 4.4; (2) cultures which had already reached an acidity of P_H 4.4 were killed by heating at 56 C. for 30 minutes and inoculated with a 24-hour culture.

In both these cases, the H-ion concentration was increased to 4.2 and 4 after 24 hours. It might be of interest to quote here the work of Hall and Frazer [29] who found that staphylococci could reach a H-ion concentration of 2.6—an end-point which exhibited no relation to saprophytic or pathogenic forms.

[29] Abstract, Lancet, 1921, 18, p. 912.

CARBOHYDRATE METABOLISM

In view of the diagnostic importance of the fermentative reaction of the colon-typhoid group, it was deemed advisable to devote considerable attention to this subject. Very little previous work has been done on the ability of the staphylococci to ferment carbohydrate mediums. Of course, it is common knowledge that they attack the more familiar sugars with the production of acid, but no gas. Gordon,[30] in reporting a classification study of the white cocci, gave the fermentation reactions on lactose, maltose, glycerol and mannitol. Dudgeon[31] reported a comparative study of the aureus and albus cocci, studying among other things their acid production in 11 carbohydrate mediums; but none of his results were quantitative. Winslow and Winslow[28] studied glucose and lactose, and Kligler[32] glucose, lactose and sucrose. More recently Winslow and his co-workers[33] made a quantitative study of the acid produced in 9 different sugars. They found more than half the strains studied fermented glucose, maltose and sucrose; about half fermented lactose; 5 strains fermented salicin, 1 strain each fermented inulin and raffinose, and no strains fermented dulcitol and mannitol.

In our study, we have employed 17 carbohydrates in all-dextrose, galactose, levulose, sucrose, lactose, maltose, raffinose, arabinose, inulin, dextrin, salicin, adonitol, mannitol, sorbitol, dulcitol, glycerol and starch. Twenty-four hour cultures were inoculated into 1% peptone broth plus 1% of the carbohydrate designated. The cultures were incubated at 37 C. for one week, and the P_H value determined by matching the tubes against the Clark and Lubs[6] standards. In table 7 the P_H values alone are given, since gas was not formed in any case.

The table shows that the carbohydrates are either fermented or not; but in either case the reaction is uniform. There are slight differences in some of the mediums, but they are not important enough for classification; they indicate merely functional differences and as such are negligible.

To compress the table:

Carbohydrates Fermented	Not Fermented
Glucose	Starch
Galactose	Dulcitol
Levulose	Adonitol
Sucrose	Dextrin
Lactose	Inulin
Maltose	Arabinose
Salicin	Raffinose
Mannitol	
Sorbitol	
Glycerol	

[30] Quoted by Winslow and Winslow. Supplement to the 34th annual report of local gov't. bd. containing the report of the Med. officer for 1904-1905, p. 387.
[31] Jour. Path. & Bacteriol., 1908, 12, p. 242.
[32] Jour. Infect. Dis., 1913, 12, p. 432.
[33] Winslow, Rothberg and Parsons: Jour. Bacteriol., 1920, 5, p. 145.

The discrepancy in uniformity of fermentation between this study and that of Winslow and others is possibly due to the fact that they included in their survey strains of Staph. epidermidis, ureae, candidus, tetragenus, candicans, aureus and aurianticus, thereby making a survey of many less active organisms than those employed in our study.

PROTEIN METABOLISM

Decomposition of Peptone to Amino Acids.—As a rule, the only accessible figures of amino acid formation of staphylococci occur scattered through bacteriologic literature where the question at hand was primarily a study of the nitrogen metabolism of several species and

TABLE 7

FERMENTATION OF CARBOHYDRATES

	Arabinose	Dextrose	Galactose	Levulose	Sucrose	Lactose	Maltose	Inulin	Dextrin	Adonite	Salicin	Mannitol	Sorbitol	Ducitol	Glycerol	Starch	Raffinose
A 1	7.4	6.2	5.9	7.0	6.2	6.2	6.2	7.8	7.1	7.6	6.0	6.2	6.0	7.7	6.0	8.0 —	7.8
A 2	7.3	4.4	4.7	5.0	5.0	5.0	4.8	7.5	7.1	7.6	6.0	4.6	4.7	7.7	6.0	8.0 —	7.7
A 3	7.2	4.6	4.7	5.0	4.8	5.6	4.8	7.5	7.1	7.6	6.0	5.0	4.7	7.7	6.0	8.0 —	7.6
A 5	7.2	4.4	4.6	5.0	4.8	5.0	4.8	7.5	7.6	7.6	5.8	5.0	4.7	7.7	6.0	8.0 —	7.8
F 1	7.0	4.6	4.6	5.0	4.9	5.0	4.8	7.5	7.8	7.6	6.0	5.4	4.7	7.7	6.0	8.0 —	7.7
H 2	7.3	4.4	4.7	5.0	4.8	5.0	4.8	7.5	7.1	7.6	6.0	5.2	4.7	7.8	6.0	8.0 —	7.7
P 1	7.3	4.4	4.7	5.0	4.6	5.1	4.6	7.5	7.1	7.6	6.0	5.0	4.7	7.7	6.0	8.0 —	7.7
P 2	7.2	4.4	6.0	5.2	4.8	5.0	4.8	7.5	7.1	7.5	5.4	5.0	4.7	7.7	6.0	8.0 —	7.8
P 3	7.3	4.5	4.7	5.2	4.8	5.0	6.0	7.5	7.1	7.6	6.0	4.6	4.7	7.7	5.0	8.0 —	7.8
P 4	7.2	4.4	4.7	5.0	4.7	5.1	5.4	7.5	7.2	7.6	6.0	4.6	4.7	7.6	5.0	8.0 —	7.8
P 5	7.3	4.9	5.1	5.2	4.9	5.1	5.6	7.5	7.1	7.6	6.2	5.4	4.7	7.7	6.0	8.0 —	7.5
S 2	7.3	4.6	4.7	5.2	4.8	5.4	4.8	7.5	7.1	7.6	6.0	4.6	4.7	7.7	6.0	8.0 —	7.7
T 1	7.3	4.4	4.7	5.0	4.8	5.0	4.8	7.5	7.1	7.8	6.0	5.3	4.7	7.6	5.2	8.0 —	7.7
T 2	7.3	4.4	4.7	5.0	4.6	5.1	4.8	7.5	7.2	7.6	6.0	5.2	4.7	7.7	6.0	8.0 —	7.7
T 3	7.3	4.4	4.7	5.0	5.0	5.0	4.2	7.6	7.2	7.6	6.2	4.6	4.7	7.7	5.0	8.0 —	7.7
T 5	7.2	4.4	4.7	5.0	4.8	5.1	4.8	7.3	7.2	7.6	6.0	4.6	4.7	7.7	6.0	8.0 —	7.7
T 6	7.3	4.6	4.7	5.2	4.8	5.0	4.8	7.5	7.1	7.6	6.0	4.6	4.7	7.7	6.0	8.0 —	7.7
T 8	7.3	4.4	4.8	5.0	4.8	5.6	4.8	7.5	7.0	7.4	6.0	4.6	4.7	7.6	5.0	8.0 —	7.6
T 9	7.3	4.6	4.9	5.0	4.8	5.2	4.8	7.5	7.1	7.4	6.0	5.2	4.7	7.7	6.0	8.0 —	7.9
X	7.3	4.4	4.7	5.2	5.0	5.0	4.8	7.5	7.1	7.4	5.4	5.4	4.7	7.0	5.0	8.0 —	7.7
Control	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0 —	7.2

one or two strains of staphylococci were fortuitously included. Our object here was to give a definite conception of the amino acid digestion of peptone, and incidentally to use such an expedient for a classification, if possible.

Rosenthal and Patai[34] found that the curve of amino acid production by staphylococcus underwent an initial sharp rise within 24 hours, and this was followed by a more gradual rate of increase until the fifth and sixth day. Also virulent organisms produced more amino acid than the avirulent ones. Their determinations were made by the Sørensen method. The work of Berman and Rettger[35] shows that at the end of 1 week 3 strains of aureus reached an

[34] Centralbl. f. Bakteriol., I, O., 1914, 73, p. 406.
[35] Jour. Bacteriol., 1918, 3, p. 367.

amino acid figure equivalent to 47 c c of 20/NaOH, and one strain of albus, a figure of 52 c c of 20/NaOH. They also used the Sørensen method.

Benton[36] recently observed that in 1.5% peptone broth, staphylococcus shows a decrease in amino acidity until the 5th day, with a following rise until the 7th day; in 2% peptone broth, the decrease continues until the 3rd day with a gradual increase until the 9th day; in pure ascitic fluid, after a 1 day decrease, there is a rise until the 4th day. She used the Van Slyke method for amino acid determination.

In our own experiment, a 2% Difco peptone extract broth was employed. The tubes were inoculated with a 24-hour growth and at the end of each day the amino acidity was determined by the Sørensen method (table 10).

TABLE 8

Amino Acid Decomposition of Peptone [*]

	1st Day		2d Day		3d Day		4th Day		5th Day	
	P_H	A. A.	P_H	A. A.	P_H	A. A.	P_H	A. A.	P_H	A. A.
A 1	7.5	40.0	7.5	48.0	7.5	72.0	7.5	100.0	7.5	44.0
A 2	7.5	60.0	7.7	48.0	7.6	84.0	7.7	112.0	7.9	72.0
A 3	7.5	68.0	7.7	68.0	7.7	88.0	7.7	116.0	7.9	72.0
A 5	7.5	80.0	7.5	72.0	7.6	92.0	7.6	120.0	8.0	76.0
F 1	7.5	68.0	7.5	72.0	7.8	96.0	7.8	120.0	8.0	60.0
H 2	7.5	68.0	7.5	96.0	7.7	112.0	7.8	116.0	8.0	72.0
P 1	7.8	56.0	7.9	56.0	7.8	96.0	7.8	116.0	8.0	72.0
P 2	7.7	56.0	7.7	80.0	7.7	96.0	7.7	116.0	8.0	72.0
P 3	7.5	56.0	7.9	84.0	8.0	96.0	7.7	116.0	7.7	64.0
P 4	7.5	56.0	7.9	72.0	7.9	100.0	7.7	92.0	7.7	68.0
P 5	7.3	52.0	7.4	68.0	7.5	76.0	7.5	76.0	8.0	64.0
S 2	7.7	48.0	7.8	76.0	7.8	72.0	7.8	92.0	8.0	80.0
T 1	7.8	80.0	7.9	116.0	7.9	116.8	8.0	140.0	8.0	68.0
T 2	7.5	56.0	7.9	84.0	7.9	96.0	7.9	80.0	8.0	68.0
T 3	7.5	56.0	7.9	72.0	7.9	96.0	7.9	96.0	8.0	68.0
T 5	7.5	56.0	7.6	72.0	7.8	88.0	7.5	80.0	8.0	40.0
T 6	7.5	56.0	7.8	68.0	7.7	92.0	7.7	72.0	7.9	60.0
T 8	7.7	56.0	7.9	116.0	8.0	116.0	7.7	132.0	7.7	104.0
T 9	7.6	44.0	7.7	80.0	7.8	100.0	7.8	72.0	7.9	64.0
X	7.8	52.0	7.8	72.0	7.8	92.0	7.8	116.0	8.0	64.0
Control	7.0	48.0	7.0	48.0	7.0	48.0	7.0	48.0	7.0	48.0

[*] In P_H column, P_H readings are given. In A. A. column, figures represent number of c c of 20/N NaOH required to neutraliz 100 c c of culture.

The significant features brought out are that at the end of the first day there is either a slight increase or decrease in amino acid, then a gradual rise to the 4th day, with a falling off on the 5th day. At the time, we assumed that a maximum had been reached on the 4th day. This checks fairly well with the results of Rosenthal and Patai, but brings our maximum a bit sooner than was the case in Benton's work.

These results differ materially from those obtained with serum broth, but the mediums were of course different. It would seem that in serum broth the amino acids are simultaneously formed and utilized,

[36] Jour. Infect. Dis., 1919, 25, p. 231.

and thus the figures are kept low; whereas in peptone broth, the amino-acidity figures increase rapidly due to the greater amounts of peptone present.

Production of Ammonia.—This test was performed for a double purpose: In the first place, it was interesting to determine what happened to the amino acid formed, and in the second place, to determine whether any differentiation could be made on this basis. The amount of ammonia formed was measured daily for 5 days after incubating at 37 C. The medium employed was composed of 1% peptone and 0.05% K_2HPO_4. The tubes were sealed with paraffin to prevent the escape of ammonia. The determination was made with Nessler reagent, and the cultures were matched against a known standard by

TABLE 9
AMMONIA FORMATION

	2d Day	3d Day	4th Day	5th Day
A 1	6.4	9.72	11.60	21.84
H 2	13.80	19.20	20.40	14.64
H 3	12.00	17.76	20.50	16.44
H 5	12.00	15.36	23.40	16.92
F 1	9.60	20.40	24.00	26.04
H 2	14.16	21.84	27.04	21.00
P 1	12.84	14.60	16.80	16.78
P 2	12.60	14.60	19.20	21.84
P 3	9.60	21.60	30.00	21.84
P 4	17.16	20.40	30.00	32.88
P 5	9.60	14.16	15.48	30.00
S 2	12.96	14.40	28.20	24.00
T 1	24.00	27.00	48.00	48.00
T 2	13.32	30.00	32.88	21.36
T 3	16.78	23.20	24.00	14.64
T 5	14.76	21.60	32.80	28.20
T 6	14.16	17.96	32.80	28.56
T 8	32.80	38.40	64.80	57.12
T 9	14.60	16.68	32.80	14.60
X	19.20	23.40	24.00	16.44
Control	1.98	1.98	1.98	1.98

Figures represent mg. of NH_3 as nitrogen per 100 c c of culture.

means of the Dubosq colorimeter. From table 9 it will be seen (1) that all the cultures produce ammonia, and (2) that amino-acidity and ammonia formation are simultaneous processes. Winslow, Rothberg and Parsons report positive ammonia formation in all but 11 strains out of 180 studied.

Reduction of Nitrates. — Gordon[30] and Winslow,[28] Rothberg and Parsons[33] found that nitrate reduction by staphylococci was a more or less general character. Winslow and Winslow[28] reported only 21% aureus and 13% albus reducers. Kligler's study showed 7 out of 11 aureus and only 1 out of 12 albus reduced nitrates. The more recent work of Winslow, Rothberg and Parsons[33] had the advantage of better technic and should have the greatest weight.

In making our determination, the medium contained 1% peptone, 0.5% K_2HPO_4 and 1% KNO_3. The cultures were incubated for one week at 37 C., and the presence of nitrates was determined by the sulphanilic acid—a—naphthalamine method. All the strains except A were able to reduce nitrates.

Formation of Indol.—In a survey of the literature of indol production by staphylococci, 3 references have been found of a positive nature. Emmerling[38] described the production of indol afer 14 days' cultivation under anaerobic conditions on an egg white medium. Tissier and Martelly[39] reported positive indol by a culture of Staphylococcus albus isolated from meat, and cultivated in a fibrin medium. Distaso[40] isolated an atypical staphylococcus which was an obligate anaerobe and showed inability to attack any sugar, but which was capable of forming indol. The results of the first two are questionable on account of the technic employed, while the third case is concerned with an atypical organism. On the other hand, negative indol production is reported by Buard,[41] Seltzer,[42] Dobrowski,[43] Distaso,[44] Zipfel,[45] Herzfeld and Klinger,[46] Winslow, Rothberg, and Parsons,[38] and Bayne-Jones and Zimmiger.[47]

Our tests were made by cultivating in a medium of 1% peptone and 0.5% K_2HPO_4 at 37 C. Tests for the presence of indol were made on the first, third, fifth, seventh and tenth day after incubation by the para-dimethyl-amido-benzald-benzaldehyde method. All tests were negative.

Action on Milk.—Table 10 gives the reaction of each strain in litmus milk. It will be seen that after 10 days' incubation at 37 C., one strain shows no apparent change in reaction, 11 strains show acid production, and 8 strains show acid with coagulation and liquefaction. The P_H values in lactose broth has been placed alongside the milk reactions. As was expected, the reaction coincides.

Liquefaction of Gelatin.—In determining gelatin liquefaction, an effort was made toward a quantitative study. The technic employed was to inoculate gelatin tubes with 0.1 c c of a 24-hour broth culture (diluted if necessary to insure an even turbidity). The amount of gelatin liquefied was measured by determining the number of c c from a mark drawn at the original level of the gelatin to the level of the

[38] Berlin der Deutsch. Chem. Gessellsch., 1896, 29, p. 2721.
[39] Ann. de l'Inst. Pasteur., 1910, 24, p. 865.
[40] Centralbl. f. Bakteriol., I, O., 1912, 62, p. 433.
[41] Compt. rend. Soc. de biol., 1908, 65, p. 158.
[42] Centralbl. f. Bakteriol., I, O., 1909, 51, p. 465.
[43] Ann. de l'Inst. Pasteur., 1910, 24, p. 595.
[44] Centralbl. f. Bakteriol., I, O., 1911, 59, p. 102
[45] Ibid., 1913, 67, p. 572.
[46] Ibid., 1915, 76, p. 1.
[47] Bull. Johns Hopkins Hosp., 1921, 32, p. 299.

nonliquefied gelatin. The cultures were incubated at 20 C. for 21 days unless the gelatin was entirely liquefied before that time, when the liquefaction was estimated.

TABLE 10

SHOWING ACTION ON MILK

	1 Day	3 Days	5 Days	7 Days	10 Days	Lactose
A 1.........	No change	No change	No change	No change	No change	6.2
A 2.........	Acid	Acid	Acid	Acid	Acid	5.0
A 3.........	Acid	Coagulation	Coagulation	Liquefaction	....	5.6
A 5.........	Acid	Coagulation	Coagulation	Liquefaction	....	5.0
F 1.........	Acid	Coagulation	Coagulation	Liquefaction	....	5.0
H 2.........	Acid	Coagulation	Coagulation	Liquefaction	....	5.0
P 1.........	No change	Acid	Acid	Acid	Acid	5.1
P 2.........	No change	No change	Acid	Acid	Acid	5.0
P 3.........	No change	Acid	Acid	Coagulation	Liquefaction	5.0
P 4.........	Acid	Acid	Acid	Acid	Acid	5.1
P 5.........	Acid	Acid	Acid	Acid	Acid	5.1
S 2.........	No change	No change	No change	Acid	Acid	5.4
T 1.........	No change	Acid	Acid	Coagulation	Liquefaction	5.0
T 2.........	No change	No change	No change	Acid	Coagulation	5.1
T 3.........	No change	Acid	Acid	Acid	Acid	5.0
T 5.........	No change	No change	No change	No change	No change	5.1
T 6.........	No change	No change	No change	Acid	Acid	5.0
T 8.........	Acid	Acid	Acid	Acid	Acid	5.6
T 9.........	Acid	Acid	Acid	Acid	Coagulation	5.2
X...........	Acid	Coagulation	Liquefaction	Acid	....	5.0

TABLE 11

LIQUEFACTION OF GELATIN

	Amount Liquefied	No. of Days
A 1...	No liquefaction	21
A 2...	5.2 c c	19
A 3...	No liquefaction	21
A 5...	7.1 c c	19
F 1...	No liquefaction	21
H 2...	No liquefaction	21
P 1...	6.0 c c	19
P 2...	1.0 c c	21
P 3...	5.5 c c	18
P 4...	No liquefaction	21
P 5...	No liquefaction	21
S 2...	3.0 c c	19
T 1...	6.7 c c	17
T 2...	5.5 c c	17
T 3...	0.9 c c	21
T 5...	3.8 c c	19
T 6...	No liquefaction	21
T 8...	No liquefaction	21
T 9...	4.1 c c	21
X..	2.0 c c	21
Control...	No liquefaction	21

Manner of Liquefaction: Some time later the study of gelatin liquefaction was extended by an observation of the manner of liquefaction. Table 12 gives a graphic representation of the findings. Up to the 10th day, let us say, there is a pseudodifferentiation of 2 types: one type giving a saucer-shaped liquefaction and the second type giving

a cone-shaped liquefaction. After that the liquefaction proceeds uniformly in all the cultures by stratification. The difference, however, is so superficial that we would hardly suggest a classification on this characteristic.

One significant feature brought out by the tables is the ability of six cultures to attack gelatin-cultures which did not a year previously manifest this ability. This shows above all the variability of the organisms to be classified—a variability which emphasizes the fact that in order to classify staphylococci we must depend on more substantial characters than functional differences.

TABLE 12

RESULTS OF AGGLUTINATION [*]

	Serums				
	A 1	A 5	P 1	T 9	L 1
A 1	5120	0	20	40	20
A 2	0	2560	1280	0	1280
A 3	0	2560	1280	0	1280
A 5	0	2560	1280	0	1280
F 1	1280	20	20	40	20
H 2	80	320	320	0	1280
P 1	0	2560	1280	20	1280
P 2	1280	0	0	0	0
P 3	0	2560	640	2560	1280
P 4	80	640	320	0	640
P 5	0	320	640	40	1280
S 2	1280	0	0	0	0
T 1	0	2560	640	0	1280
T 2	640	2560	640	320	1280
T 3	0	2560	1280	0	1280
T 5	640	20	0	0	1280
T 6	0	2560	1280	40	0
T 8	640	0	0	20	40
T 9	640	2560	1280	640	1280
X	1280	2560	640	1280	1280
C 15	2560	160	80	80	20
C 16	640	0	20	20	20
C 18	640	0	20	20	20
J 1	80	1280	1280	80	1280
L 1	0	1280	1280	0	1280

[*] Figures represent the dilution at which agglutination was observed by naked eye reading. All controls were negative.

Reduction of Methylene Blue.—At the December, 1921, meeting of the Am. Assn. of Bacteriol., Avery reported his investigation of the use of methylene blue in differentiating hemolytic streptococci from human and dairy sources. He found that dairy strains—bovine and cheese—reduced methylene blue, but that the human strains did not. Because of these results, we tried reducing methylene blue by our staphylococcus strains. The technic of the test consisted in adding to a 24-hour broth culture varying dilutions of methylene blue, and covering with sterile paraffin. The cultures were reincubated for a second day,

when the results were read. It was found that all strains reduced or decolorized methylene blue at dilutions of 1 : 50,000 and 1 : 25,000; they showed partial decolorization at dilution of 1 : 10,000, except strains T8, C15 and J1, which were negative; and at a dilution of 1 : 1,000 all the strains were negative.

Hydrolysis of Sodium Hippurate.—Ayers and Rupp [48] found that hemolytic bovine streptococci could be differentiated from the human by the fact that the former could split sodium hippurate into glycocoll and benzoic acid. We employed this test in our study to determine whether such a procedure would be of value in differentiating the staphylococci. The medium employed contained 1% peptone, 1% sodium hippurate 0.015% K_2HPO_4, and the reaction was adjusted to P_H 7.2. The cultures were incubated at 37 C. for 7 days. At that time hydrolysis was determined by adding 0.5 c c of a 7 % $FeCl_3$ solution for every 2 c c of the culture medium; if hydrolysis had taken place an insoluble precipitate was formed, whereas the mixture became clear on standing several minutes if hydrolysis had not taken place. All the cultures were able to split sodium hippurate.

RELATION TO VIRULENCE

Although Neisser and Wechsberg [2] showed that aureus and albus strains alike are capable of hemolytic activity, their experiment seems to indicate that purely saprophytic forms never attain this faculty. This was corroborated later by Kutcher and Konrich [22] and also by Koch.[23] Noguchi in presenting his results stated that hemolysis was proportional to the virulence of a strain, but the evidence he presents does not justify such a conclusion. Montegazza [49] was unable to demonstrate any definite relation between the intensity of an infection and the quantity of hemolysin produced.

In approaching an answer to the question of inter-relationship between virulence and hemolysis, two methods present themselves—either hemolytic strains will prove to be virulent, or nonhemolytic strains will be avirulent.

Following the first method, then, strains A5, P1, P3 and T9, all definitely hemolytic, were used. Twenty-four-hour broth cultures of each were inoculated in 1 c c quantities into the peritoneum of separate mice. No causalties occurring, the mice were killed, the peritoneums were washed with sterile saline, and the washings injected into a fresh mouse. Incidentally, cultures were made of the peritoneal exudate and heart blood as a check. This procedure was carried successively for

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[48] Personal communication.
[49] Biochem. Centralbl. 1908, 8, p. 226.

3 days with 3 mice for each strain. After the third mouse, in no case was staphylococcus demonstrable by smear or culture from the peritoneum indicating complete overwhelming of the 4 strains. Cultures of the heart blood, which were made to test the invasive powers of the 4 strains, were negative each day. Here, if anything, the virulence of the strains should have increased by the animal passage, but instead the organisms decreased, the more resistant organisms lasting until the third passage. This would indicate that hemolysis is quite independent of virulence.

Later, in attempting to isolate a virulent strain, 3 different strains from pus were injected into rabbits. Two strains injected intravenously in amounts of 3 c c of a 24-hour broth culture caused no apparent effect. The third strain caused death in 0.5 c c amounts within 2 days, and 0.25 c c amounts within 1 week, presenting in this case typical staphylococcus lesions. This strain was used in our serologic work and designated as L1. The point of interest here, however, is that although the 3 strains were distinctly hemolytic, only 1 proved to be sufficiently virulent to kill a rabbit. The combined evidence of these 7 strains makes plausible the conclusion that hemolytic strains are not necessarily virulent.

The second method—that nonhemolytic strains would prove to be avirulent—was not tried. Nonhemolytic strains were not isolated during the course of the entire investigation. However, a glance at table 4 at this point will show that strains of an undoubtedly saprophytic character are hemolytic. In a general way, perhaps, the strains requiring the greatest time for hemolysis are probably the least virulent of any; but, on the other hand, the strains giving most rapid hemolysis may be saprophytic.

LEUKOCIDIN ACTIVITY

It was not the purpose in this experiment to make a study of the leukocidin produced by staphylococci. The subject has been well worked out. The purpose was rather to determine whether hemolytic activity bears any relation to leukocidin activity.

Van de Velde[50] first demonstrated leukocidin by filtration in 24-hour cultures. Later he and Denys[51] showed that the leukocidin was not specific, but was a metabolic product which destroyed other tissue cells as well as leukocytes. Bail[52] obtained a maximum production of leukocidin in 11 days. Neisser and Wechsberg[2] added considerably to the knowledge of staphylococcus leukocidin. Making use of the reduction of methylene blue by leukocytes, they found that leukocidin appears in filtrates after 4 days and reaches

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[50] La Cellule, 1894, 10, p. 403.
[51] Ibid., 1895, 11, p. 395.
[52] Arch. f. Hyg., 1898, 32, p. 133.

a maximum after 1 week; that leukocidin was produced by white and orange strains; that the more virulent the strain the more leukocidin produced; that leukocidin was destroyed by heating at 56 C.; that normal horse and immune serum possesses antileukocidin; that leukocidin does not attack kidney cells.

In making our tests the same strains used for hemolytic activity were used. The cultures were inoculated each day into 10% serum broth for 16 days so that on the 17th day we had 16 cultures of each strain of from 1 day to 16 days old. The cultures were then centrifuged at high speed for 5 minutes, and 1 c c of the supernatant fluid was used for the test.

Leukocytes were obtained by injecting 8-10 c c of sterile aleuronat into the pleural cavity of guinea-pigs, and after 15 hours the animals were bled to death and the pleural exudate removed with a capillary pipet. An equal amount of 1.5% sterile sodium citrate was added to the cells to prevent coagulation.

The presence of leukocidin was determined by the methylene blue reduction test. The methylene blue consisted of 1 c c saturated solution of methylene blue, 20 c c absolute alcohol, and 29 c c distilled water. The minimum quantity of leukocytes to reduce methylene blue was first measured by using different amounts of leukocytes varying from 0.2 c c to 2 c c, the volume being made equal through the series with sterile salt solution. Two drops of methylene blue were added, and then the mixture was covered with a layer of sterile liquid paraffin to prevent reoxidation from the air. The tubes were incubated at 37 C. for 2 hours.

To twice the minimum quantity of the leukocytes found necessary to give reduction of methylene blue was added 1 c c of the super-natant centrifuged culture. The tubes were incubated at 37 C. for 1½ hours, when 2 drops of methylene blue and liquid paraffin were added. Incubation was continued for 2 hours more when the readings were made. In case of reduction, no leukocidins were present, since the leukocytes had not been injured.

It was found that leukocidin appeared on the 4th day and disappeared on the 8th day; and that only strains H2 and T9 produced leukocidins. Thus it is seen that H2, which did not show hemolysin production in broth cultures, produces most leukocidin, and A5, which produced most hemolysins, does not produce leukocidins. A1 is negative in both cases, while T9 is positive in both cases. However, strains A5 and H2 indicate distinctly that hemolytic and leukocidin activity are not dependent on each other.

Theoretically we would expect that the amount of leukocidin produced would bear a relation to the virulence of a strain, for the latter would depend to some extent on the former. Since virulence and hemolysis were found to be individual characters, it was hardly supposed that hemolysis would show any dependence on leukocidin production.

III. SEROLOGIC REACTIONS

As a final analysis, recourse was taken to differentiate the hemolytic staphylococci on a serologic basis. The impression is that although biochemical reactions may vary, serologic reactions if once positive will always remain positive. So, for example, the agglutinability of an organism may fluctuate quantitatively, but not qualitatively. For no other reason, then, this part of the work seemed to have the greatest promise. Both deviation of complement and agglutination tests were made, and the agglutination tests were supplemented by absorption tests.

In preparing immune serums, strains A1, A5, P1, T9 and L1 were employed. Salt suspensions were made from agar slants and rabbits were injected intravenously in 3 day periods, with 2 days between each period. Five-tenths c c of the suspensions was injected the first period, and this was increased 0.5 c c each period until a serum of sufficiently high titer was obtained.

COMPLEMENT FIXATION

The literature on the complement fixation of staphylococci is scant. The one reference available was that of Kolmer, Trist and Yagle [53] in relation to influenza. Using a Staphylococcus aureus antigen, they were unable to get fixation with either normal or influenza serum.

The antigens used in these experiments were suspensions of 24 cultures to which were added 0.1% formaldehyd. The preparation of the serum has already been described.

After going through the preliminaries of obtaining antigenic and complementary doses, the tests were made by incubating at 37 C. It was found that all 5 serums gave fixation with all of the antigens. There appears to be no qualitative differentiation of the different strains.

One more step was taken, and that was to determine whether there might be quantitative separation into groups by complement fixation. Four strains were picked at random, and the serum used in dilutions of 1:50, 1:100, 1:150. The results did not warrant extending the

[53] Jour. Infect. Dis., 1919, 24, p. 583.

work to include all the strains. No sharp difference in the ability of the strains to fix complement was manifested, as the serums were increased in dilution.

It would seem, therefore, that staphylococci are able to fix complement in more or less the same degree. Further, the reaction is a specific one for antigens prepared of streptococci and B. friedländer were unable to prevent hemolysis. But no evidence is given of a possible classification of staphylococci by complement fixation—either in a qualitative or quantitative way.

This is not in the least surprising, however, when we recall that complement fixation does not show divisions into groups with those cocci which have been proved to be of different serologic types by agglutination reactions.

AGGLUTINATIONS

The agglutination reactions of the staphylococci have been studied by several investigators. Kolle and Otto [20] found that immunized serum distinguished the pathogenic from the nonpathogenic forms. This was confirmed by Klopstock and Bockenheimer,[53a] Van Durme,[3] Proscher,[54] Kutscher and Konrich,[22] Veiel,[55] Fraenkel and Baumann [56] and Montegazza.[49] Trincas [57] states that serum prepared with hemolytic strains shows strong agglutination with hemolytic strains, and slight agglutination with nonhemolytic strains; and vice-versa. Walker and Adkinson [58] found that an aureus immune serum would agglutinate aureus and not albus strains; and that an albus immune serum would agglutinate albus and not aureus strains.

Our object was to group staphylococci by agglutination into as many serologic groups as would evidence themselves, without regard to virulence or pigment. The same serums used in the complement-fixation test were used for agglutination, and the same antigens also, except that they were diluted until their turbidity equaled that of the Dreyer standard for the typhoid group agglutinations. The agglutinations were set up in serum dilutions of 1 : 10 and going as far as was necessary to include the agglutination titer of the respective serums. The serum dilutions and antigens were added in 0.5 c c amounts each, and incubation was effected in a water bath at 56 C. for 16 hours.

In table 12 the figures represent the dilution at which final agglutination was observed with naked eye. There was present in the serums a proagglutinoid zone.

An analysis of the table shows that serum A1 agglutinates strains A1, F1, P2, S2, T2, T5, T8, T9, X, C15, C16 and C18. Serums A5,

[53a] Centr. f. Bakt., 1903, 34, p. 437.
[54] Arch. f. klin. Chir., 1903, 72, p. 325.
[55] München. med. Wchnschr., 1904, 51, p. 13.
[56] Ibid., 1905, 52, p. 937.
[57] Biochem. Centralbl., 1908, 8, p. 609.
[58] Jour. Med. Res., 1917, 35, p. 373.

P1, and L1 agglutinate strains A2, A3, A5, H2, P1, P3, P4, P5, T1, T2, T3, T6, T9, X, J1, and L1. Serum T9 agglutinates P3, T2, T9 and X. Serums A5, P1 and L1 are unquestionably the same since they give the same reactions. It will be noted that strains T2, T9 and X are agglutinated by all the serums, and P3 by all the serums except A1. Aside from these atypical agglutinations, the strains fall definitely with one serum. Apparently, then, the agglutination tests give the following grouping:

I.—A1, F1, P2, S2, T5, T8, C15, C16, C18.

II.—A2, A3, A5, H2, P1, P4, P5, T1, T3, T6, J1, L1.

III.—T2, T9 X and possibly P3.

TABLE 13

RESULT OF ABSORPTION TESTS ANTIGENS *

	Serum Absorbed With						
	A 1-A 1	A 1-X	T 9-P 3	T 9-T 2	L 1-A 5	L 1-P 3	L 1-T 9
A 1............	0	4800	—	—	—	—	—
A 2............	—	—	—	—	0	300	600
A 3............	—	—	—	—	0	300	600
A 5............	—	—	—	—	0	300	600
F 1............	0	+	—	—	—	—	—
H 2............	—	—	—	—	600	300	600
P 1............	—	—	—	—	0	300	+
P 2............	0	+	—	—	—	—	—
P 3............	—	—	0	2400	600	0	1200
P 4............	—	—	—	—	0	300	+
P 5............	—	—	—	—	0	300	+
S 2............	0	+	—	—	—	—	—
T 1............	—	—	—	—	0	300	+
T 2............	—	0	0	0	300	0	0
T 3............	—	—	—	—	0	300	+
T 5............	0	+	—	—	—	—	—
T 6............	—	—	—	—	0	300	+
T 8............	0	+	—	—	—	300	+
T 9............	0	0	0	0	300	0	0
X............	600	0	0	150	600	0	0
C 15..........	0	+	—	—	—	—	—
C 16..........	0	+	—	—	—	—	—
C 18..........	0	+	—	—	—	—	—
J 1............	—	—	—	—	0	300	+
L 1............	—	—	—	—	0	600	1200

* — indicates that strain did not agglutinate prior to absorption; figures represent dilution of final positive agglutination; + indicates no test. All controls were negative.

ABSORPTION TESTS

In order to further identify the groups suggested by the agglutination reactions absorption tests were conducted, employing the technic of Small and Dickson.[59] One c c of a 1 : 10 dilution of the immune serum was mixed with 4 c c of the concentrated antigen in a sterile centrifuge tube. This amount of the antigens was found sufficient to

[59] Jour. Infect. Dis., 1920, 26, p. 230.

absorb the homologous agglutinins after 4 hours' incubation at 37 C., the tubes being shaken at half-hour intervals. After this period of incubation the tubes were centrifugalized and the supernatant serum dilution (1:50) was drawn off and agglutinations carried out as described.

Serum A1 was absorbed with strain A1 and X; serum T9 with P3 and T2; serum L1 with A5, P3 and T9, and agglutinations performed against the antigens which agglutinated with the respective serum before absorption. The results are presented in table 13.

The absorption tests confirm the groups found by agglutination. Group 1 remains as was found, but in group 2, H2, is placed in a subgroup because although it agglutinates with the same serums as A5, absorption by A5 does not remove agglutinations for H2. In group 3, P3 is placed in a subgroup. P3 removes agglutinins for all members of group 3, but the other members of group 3 do not remove agglutinins for P3.

Revising our classification, then, we would have:

Group 1	Group 2	Group 3
A 1	A 2	T 2
F 1	A 3	T 9
P 2	A 5	X
S 2	P 1	Subgroup
T 5	P 4	P 3
T 8	P 5	
C 15	T 1	
C 16	T 3	
C 18	T 6	
	J 1	
	L 1	
	Subgroup	
	H 2	

DISCUSSION OF SEROLOGIC REACTIONS

The use of complement fixation in determining types among the staphylococci appears to be worthless. Although staphylococci do fix complement, no grouping appeared possible, either quantitatively or qualitatively. Nor is this surprising—on the contrary, it is more or less what was to be expected. Complement fixation has been disappointing in its inability to differentiate types—probably because the immunity established although specific for the particular species is general and not sufficiently specialized to detect individual types.

Agglutination, however, has already been proved to be an efficacious means of detecting types. Furthermore, agglutination is a fixed quality, and one which is considered reliable. So that, when the statement is

made that virulent types agglutinate only with serums prepared from virulent strains, there must be an error somewhere. The properties of virulence are obviously among the most unstable of bacterial characters. Culture on laboratory mediums renders a virulent strain nonpathogenic in a very short time. Yet it is scarcely conceivable that the immunity reactions are as readily modified. By way of illustration: Strain L1, which was distinctly pathogenic, was used for the preparation of immune serum before it could have undergone avirulence; but its serum did agglutinate other strains, including A5, P3 and T9, all 3 of which were proved nonpathogenic. It may be that A5, P3 and T9 were pathogenic at some time or another, but at the time the test was made they were not pathogenic. It seems clear to us that virulence does not dictate the group into which a staphylococcus shall fall.

Nor does it seem plausible that hemolytic activity is the basis of agglutination grouping. We have been unable to obtain absolutely non-hemolytic cultures, and have been unable to establish this point conclusively. However, we were able to get these groups among hemolytic organisms, whereas if hemolysis were the fundamental of the grouping, we should have obtained agglutination of all our strains by all our serums.

Regarding the association of pigment and agglutination, this much can be said: Occasionally, there may develop on a plate streaked with a pure culture, colonies varying appreciably in intensity of pigment, from which, as Sullivan [60] has shown, quite distinct types may be derived by selection of the extremes. Yet it does not seem probable that the parent strain in such a case would vary from its successor in its agglutination reactions. More relevant, however, strain J1, which is an albus, did agglutinate with serums A5, P1 and L1, which were prepared from antigens of varying shades of orange. An analysis of the pigment and agglutination tables, with this one exception cited, bears out the contention of Walker and Adkinson [58] in a general way. The members of group 1 are of a light pigment—either white or of a light shade of yellow, which without the refined technic of Winslow and Winslow [28] would easily be called a white.

A study of the tables of the different biochemical reactions shows no definite relationship between the agglutination groups and these reactions. In a very general way Group 1 seems to contain the less active strains, but it also contains some rather active strains. Groups 2 and 3 possess none of the light pigmented nor any of the less active strains.

[60] Jour. Med. Res., 1905, 14, p. 109.

These immunologic groups will perhaps explain the variations experienced in curative and prophylactic inoculations of either the organisms or serum. Stock vaccines, for example, will not necessarily be specific, nor will immune serum prove to be efficacious unless it falls into the same group. But having determined the group or type of staphylococcus under question, we can employ specific material either prophylactically or curatively.

CONCLUSIONS

Staphylococci produce a hemolytic substance in broth which appears on the 6th day, reaches a maximum at the 9th or 10th day and then disappears between the 13th and 16th day.

This hemolytic substance · is thermolabile, is unaffected by the presence of carbohydrates and appears to be associated with proteolysis and possibly autolysis.

All cultures of staphylococci isolated during the course of this investigation appear to be hemolytic—only the time of its manifestation is in some cases considerably delayed.

Hemolytic cultures did not lose their hemolytic powers by continued transplantations into blood-free mediums for a period of more than four months.

Hemolytic activity shows no relationship to any of the biochemical reactions studied.

Staphylococci fix complement specifically, but cannot be classified by such an expedient.

Three groups seen definable of the 25 strains studied by agglutinations and absorption test, with 2 ill-defined subgroups—one each under group 4 and group 3.

These groups apparently bear no relationship to virulent hemolysis or biochemical activity. Group 1 appears to include the light pigmented and less active strains.

These groups may account for the variations experienced in the past in the use of serum and vaccines.

COMPARATIVE RESULTS OF THE LIGATION OF THE HEPATIC ARTERY IN ANIMALS

ITS APPLICATION TO MAN *

MOSES BEHREND, M.D., H. E. RADASCH, M.D.

PHILADELPHIA

AND

AMMON G. KERSHNER, M.D.

NORRISTOWN, PA.

In a preliminary report [1] the reason for this study was pointed out to be an injury of the hepatic artery sustained by a boy, aged 12 years, who was run over by a wagon, the wheels passing over the epigastric region. He had all the symptoms of an internal hemorrhage. At operation, the hepatic artery was found to be severed. Both ends of the artery were tied. The boy did well until the tenth day, when he developed a slight jaundice, accompanied by vomiting. He died on the fourteenth day, of symptoms resembling acute yellow atrophy of the liver. A postmortem examination was refused. Our desire to duplicate this injury in animals has developed these experiments.

In our preliminary studies, rabbits were used exclusively; but in our later experiments, dogs, cats, guinea-pigs and rabbits were employed. These animals may be divided into the carnivorous and herbivorous types. We found the former particularly resistant to the effects of the ligation of the hepatic artery, while the latter succumbed in every instance. This difference in their susceptibility to the ligation may be due to changes in the metabolism in these two types of animals. This problem is occupying our attention at the present time and the results will be reported in the near future.

However, the anatomic variations may be a sufficient reason alone to cause such a tremendous difference in the mortality rate of the different animals. To arrive at a definite conclusion concerning the difference in the ability of these animals to resist the ligation performed in a similar manner, a study of the comparative anatomy of the four animals used was deemed essential (Figs. 1, 2, 3 and 4). It will be

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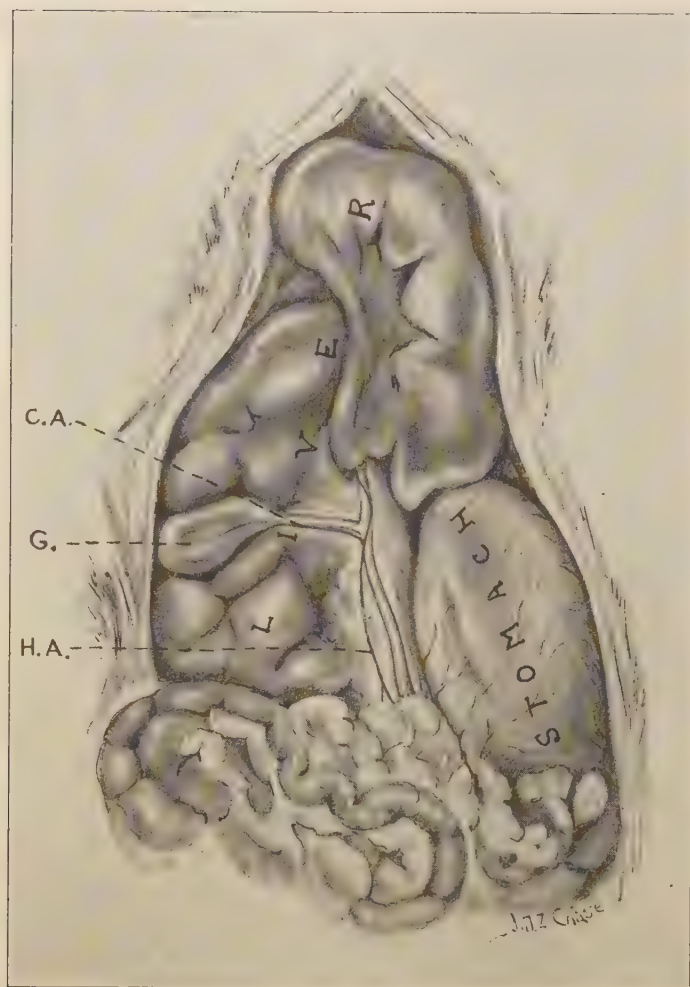1. Behrend, Moses: Surg. Gynec. & Obst. **31**:182 (Aug.) 1920.

Fig. 1.—Hepatic artery of the guinea-pig. The hepatic artery is simply a line running over the gastrohepatic omentum: *C. A.*, cystic artery; *G.*, gallbladder and *H. A.*, hepatic artery.
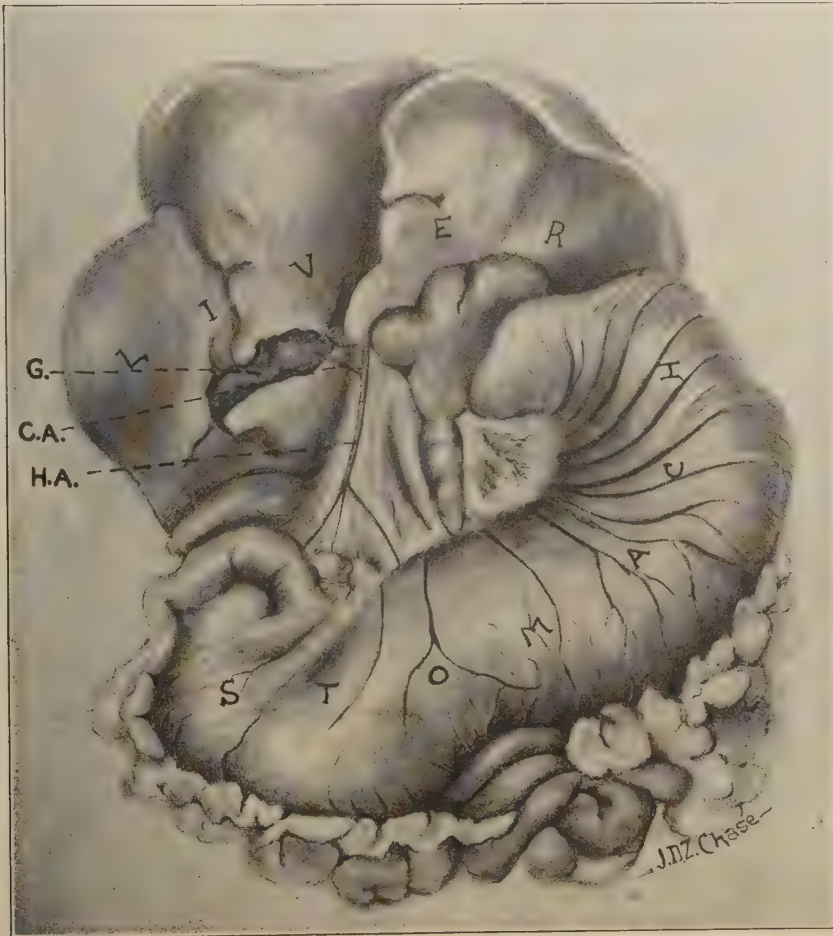
Fig. 2.—Hepatic artery of the rabbit. The single artery running over the gastrohepatic omentum may be noted: *G.*, gallbladder; *C. A.*, cystic artery, and *H. A.*, hepatic artery.

readily seen that the anastomosis of blood vessels in the cat and dog is rather intimate when compared to that of the rabbit and guinea-pig.

The anatomy of the hepatic artery and its variations in man were reported in previous papers, as well as the variations of the bile ducts.[2] These studies have shown, however, that in certain cases in which there is no anastomosis at all of the hepatic artery before it enters the liver, and in which the hepatic artery is derived from the celiac axis only, there is considerable danger in ligating the sole source of
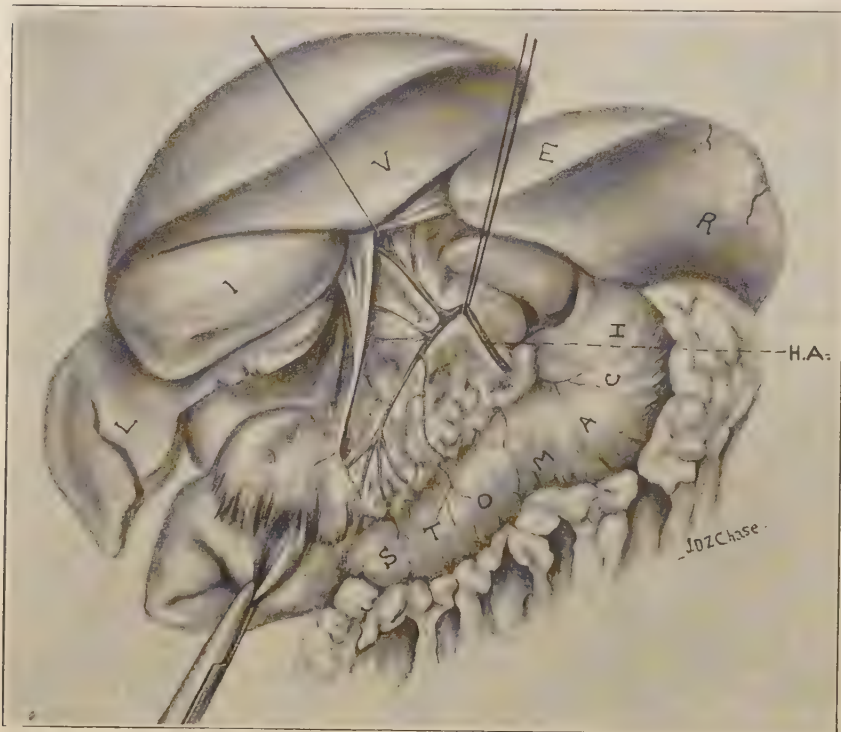
Fig. 3.—Hepatic artery of the dog. The artery runs behind the lesser omentum. The intimate anastomosis accounts for the resistance of the dog to its ligation: *H. A.*, hepatic artery.

arterial blood to the liver. This is especially true since the hepatic artery is an end artery (Figs. 5 and 6). When an accessory hepatic artery is derived from the superior mesenteric or the left gastric artery there is probably less danger to the patient, but there is no question that accidental ligation of the main vessel even in such a case exposes the patient to danger of necrosis of the liver.

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2. Behrend, M.: Failure of Surgery on Extrahepatic Biliary Passages. J. A. M. A. **73**:892 (Sept. 20) 1919; Improved Technic for Removal of Gall-bladder, J. A. M. A. **75**:222 (July 24) 1920.

Our experiments have shown that if even a branch of the hepatic artery is tied there is a microscopic change in the liver cells (Fig. 7). This change in the liver cells may still be seen weeks after the experiment has been performed. Figure 8 illustrates the microscopic changes in the liver cells of a dog, killed 113 days after the ligation. The fact that degeneration of liver cells may be detected easily by the microscope even weeks afterward may explain the cause
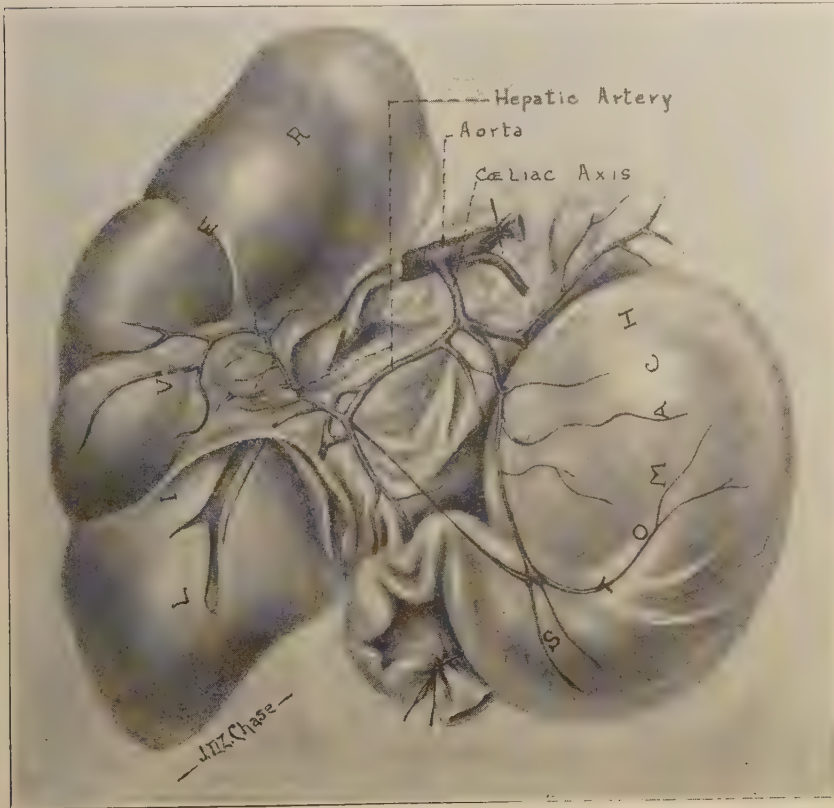

Fig. 4.—Hepatic artery of the cat. The complexity, the different branches and the anastomosis are in marked contrast to those found in the rabbit and guinea-pig.

of death of a patient who was admitted to the Mount Sinai Hospital a few months ago. About two years before admission, a cholecystectomy had been performed. The patient was brought to the hospital in an unconscious condition. Her face was tinged slightly yellow. A diagnosis of acute yellow atrophy of the liver was made, which was confirmed at necropsy. Unfortunately, before a minute dissection of the liver could be performed, the specimen was destroyed   An oppor-
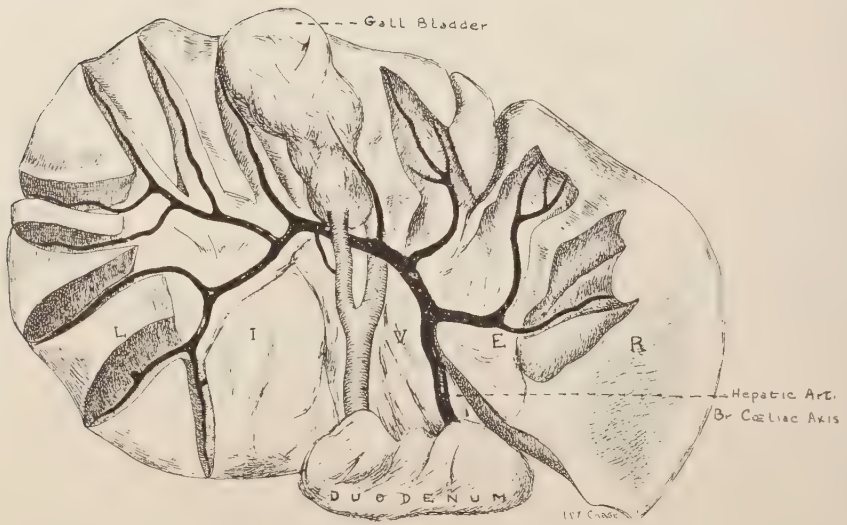
Fig. 5.—Human liver, inferior surface, illustrating the hepatic artery as a single blood vessel coming from the celiac axis. After the hepatic artery enters the liver, it terminates as an end artery without anastomosis.
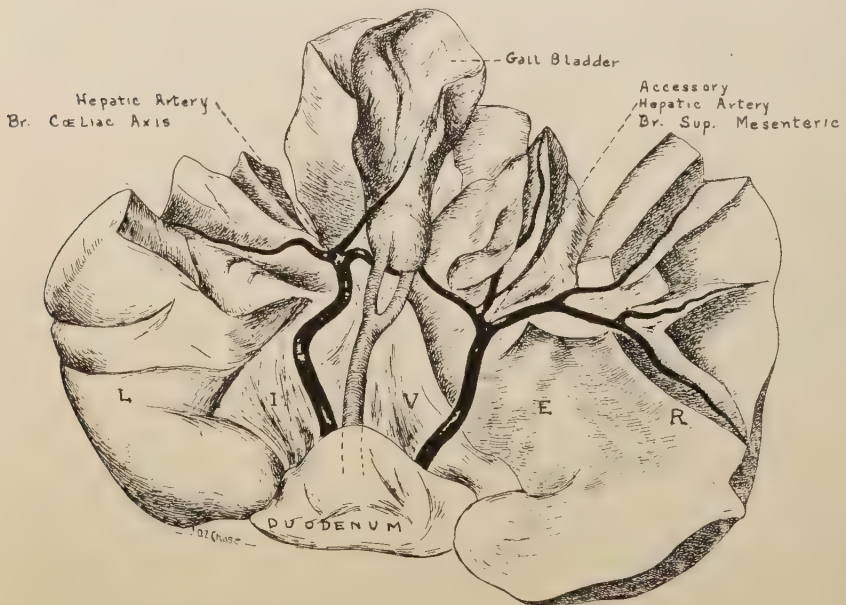

Fig. 6.—Inferior surface of human liver, showing the hepatic artery as a branch of the celiac axis; an accessory hepatic artery as a branch of the superior mesenteric artery. As in Figure 5, the liver has been dissected to show that the hepatic artery is an end artery.

tunity seldom encountered to prove our contention that ligation of the hepatic artery is fraught with the greatest danger was lost. Microscopically, the liver showed a fatty degeneration typical of acute yellow atrophy of the liver.

TABLE 1.—Sites of Ligation and Results Obtained After the Operation on the Hepatic Artery of the Rabbit

Rabbit	Site of Ligation	Death Following Operation	Death by Chloroform	Liver Changes	
				Gross	Microscopic
1	Peripheral	18 hours		No pathologic condition noted	(No sections made)
2	Peripheral	4 days		Liver shows several white areas, where tissue appears cheesy in consistency extending deeply into liver	Large area of necrosis, with peripheral zone of cellular infiltration; marked dilatation of central vein of lobules; hepatic arterioles difficult to find, and show hyalinization
3	Central		20 days	No liver changes except dense adhesions involving omentum, mesentery and under surface of liver	(No sections made)
4	Peripheral	5 days		Massive necrosis in area similar to Rabbit 2	(No sections made)
5	Peripheral including Portal Vein	17 hours		Anemic, pale and flabby	Necrosis of cells near central part of lobules; cells stained poorly; collapse of cells
6	No Vessel Ligated	Died during operation		Normal	(No sections made)

As has been stated, the site of ligation of the hepatic artery and its branches is important in developing the conclusions of our study. Let us divide the steps of a ligation into the central and peripheral, or a combination of the two (Tables 1 to 6). By a central ligation is meant the ligation of the hepatic artery just as it leaves the celiac axis. By a peripheral ligation is meant the ligation of the hepatic artery
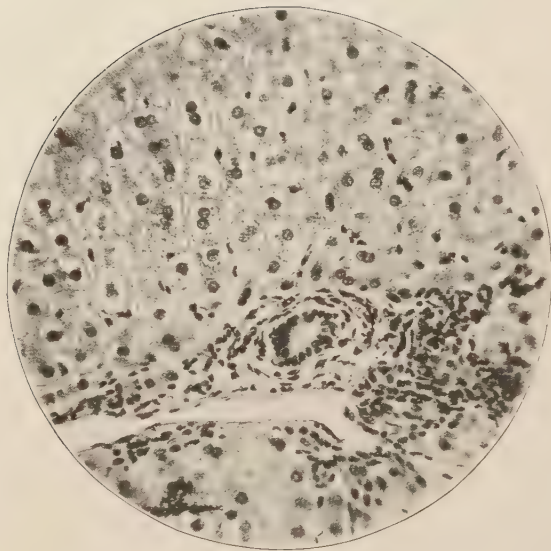
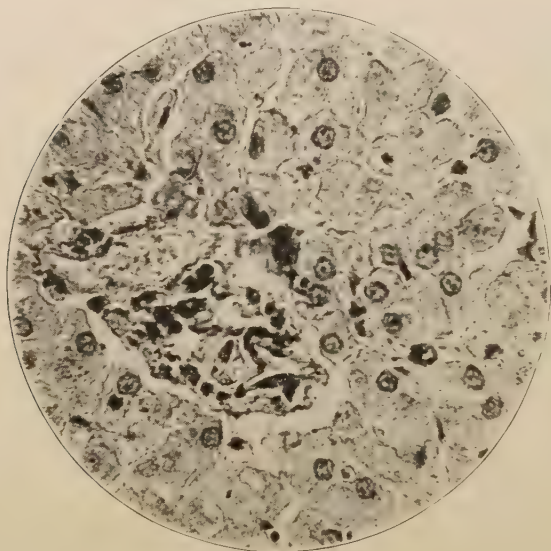Fig. 7.—Degeneration of the nuclei as a result of ligation of a branch ōf the hepatic artery (Kershner).
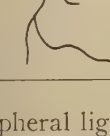

Fig. 8.—Liver of dog killed 133 days after ligation of the hepatic artery; nuclei dissolved (Kershner).

close to the liver in the folds of the gastrohepatic omentum. In a central ligation, on account of the anastomosis with the gastroduodenal and the right gastric arteries, death of the animal is not certain. This fact is confirmed in man by Chiari.[3] Rabbits and guinea-pigs may even resist a ligation of this character; but if a successful

TABLE 2.—Sites of Ligation and Results Obtained After the Operation on the Hepatic Artery of the Rabbit

Rabbit	Site of Ligation	Death Following Operation	Death by Chloro-form	Liver Changes	
				Gross	Microscopic
7	Peripheral	19 hours		No gross change noted	(No sections made)
8	Peripheral	18 hours		No color change	(No sections made)
9	Peripheral	23 hours		Massive necrosis in all but one lobe; this lobe had blood supply intact	Massive necrosis at one end of section; very little reaction against same; liver cells stained poorly; portal veins thrombosed and hugely dilated
10	Central		50 days	Extensive adhesions; several large cheesy masses encased in liver substance; color, paler than normal	Hepatic cells stained poorly; much degeneration; central veins show dilatation
11	No Vessel Ligated		18 days	Adhesions	(No sections made)
12	Peripheral	36 hours		Characteristic necrosis, especially of lobe to which gallbladder is attached; few adhesions found	Areas of necrosis, with zones of reaction against same; dilatation of portal venules

peripheral ligation is performed in herbivorous animals, such as rabbits and guinea-pigs, all die in from seventeen hours to three or four days. This confirms our experiments reported in our preliminary note. Dogs are most resistant and live in spite of the ligations, which fact coincides

3. Chiari: Quoted by Baruch, Beitr. z. klin. Chir. 45:502, 1915.

with the work of Whipple.[4] Kehr and Narath [5] state that fatal necrosis in rabbits is common because all the branches of the hepatic artery are easy to ligate, while in dogs it is very different because of numerous anastomoses and sources of blood supply from the diaphragm. In his dissections of the liver of the dog, Dr. Benjamin Lipshutz, working in our laboratory, found no arterial supply going to the liver from any source except through the agency of the hepatic artery as illustrated in Figure 3. Dogs and cats will show the effects of a ligation for several days afterward. They are not so playful and there is an appreciable loss in weight. Still they recover from the effects of the operation.
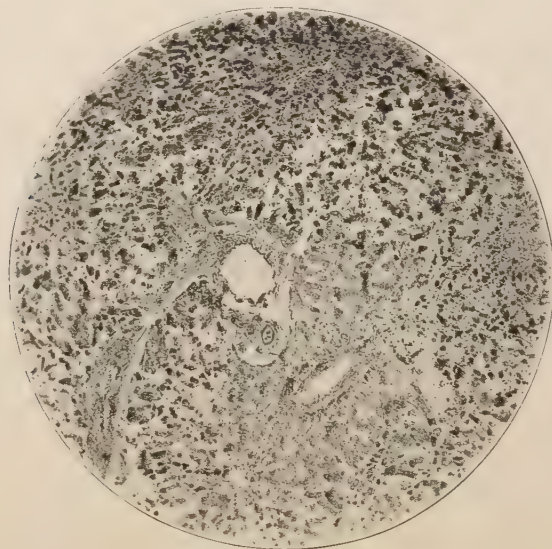
Fig. 9.—Massive necrosis of liver of cat after every vessel had been ligated that entered the liver (Kershner).

In only one cat were we able to cause death by ligation of every vessel running into the liver. This included also the ligation of the vessels of the diaphragm, which, according to some authorities, keep the animals alive after the hepatic artery has been ligated. The microscopic study of the liver of this animal showed it to be in a state of complete necrosis (Fig. 9).
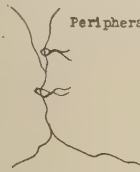
The most important deductions from our studies will be their application to the human being. Naturally the experimental operation cannot be performed in man; but from our studies in the anomalies of the hepatic artery in the anatomic laboratory and at the operating table, we are convinced that the hepatic artery instead of the cystic

4. Whipple: Bull. Johns Hopkins Hosp. **20**:281, 1909.
5. Kehr and Narath: Deutsch. Ztschr. f. Chir. **135**:305 (March) 1916.

artery may easily be ligated. It is our opinion that some unexplainable deaths are due to necrosis of the liver, caused by the ligation of the hepatic artery, especially in those cases in which there is no anastomosis before the hepatic artery enters the liver and in which there is no accessory hepatic artery.

TABLE 3.—SITES OF LIGATION AND RESULTS OBTAINED AFTER THE OPERATION ON THE HEPATIC ARTERY OF THE GUINEA-PIG

Guinea-Pig	Site of Ligation	Death Following Operation	Death by Chloroform	Liver Changes	
				Gross	Microscopic
1		12 hours		Liver soft and flabby, irregular white areas	Areas of focal necrosis, hydropic degeneration; few vessels contained coagulum
2	Peripheral	2½ days		Liver shows irregular white areas of necrosis, cheesy and friable in consistency	Typical pale infarct, zone of reaction surrounding same; portal veins dilated; rest of tissue shows congestion and cloudy swelling
3	Central	3½ days		Some adhesions, one lobe pale and anemic; small white areas of necrosis in rest of lobes; distinct anemic infarct, reaction against same being poor	Thrombus in portal vein; fatty infiltration and hydropic degeneration
4	Central		9 days	Very few adhesions; no gross changes	Cloudy swelling predominating; hydropic degeneration near central vein area; sinusoids greatly injected in places
5	Peripheral	5 days		Irregular areas of necrosis marked; adhesions profuse on under surface of liver	No area of necrosis included in section; cells generally show hydropic degeneration; arterioles difficult to find

The deliberate ligation of the hepatic artery in man has been performed by others, and it illustrates our contention that death results following the operation. Baruch,[6] in referring to an hepatic aneurysm

6. Baruch: Beitr. z. klin. Chir. **45**:502-512, 1915.

states that the ligation of the hepatic artery is tragic on account of its lethal effect. He also reports eight deliberate ligations of the hepatic artery. Tuffier,[7] in operating on what was supposedly a hydatid cyst, opened an aneurysm of the hepatic artery. The bleeding that followed was so profuse that he was compelled to ligate the hepatic artery proximal to the aneurysmal sac. Death followed within four days. There was
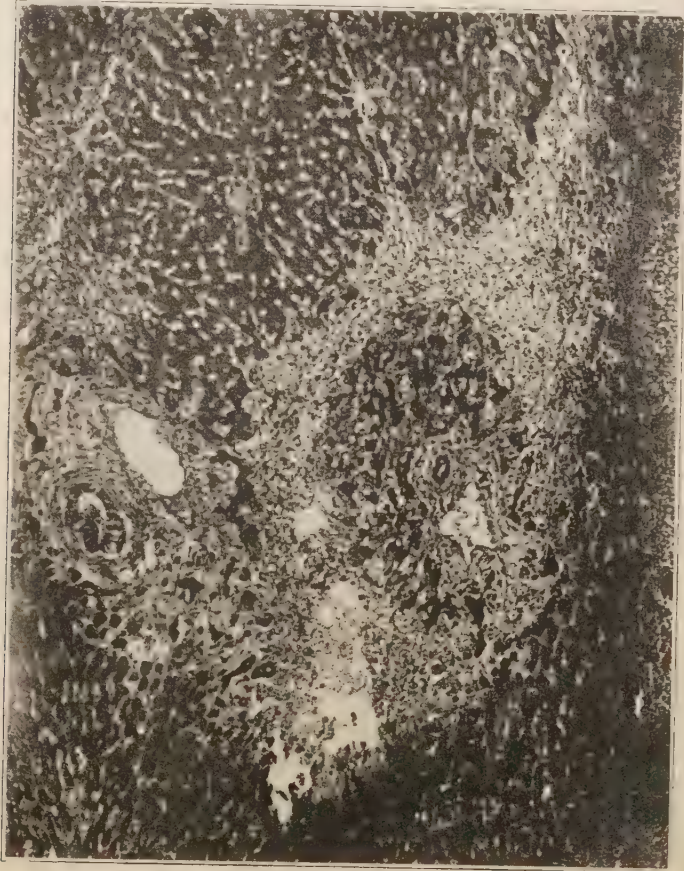
Fig. 10.—Necrosis and degeneration of liver cells and cloudy swelling (Radasch).

no liver necrosis; but death was thought to be due to hepatic insufficiency. Kehr's[8] patient is the only one, whose case is reported, that lived after the ligation of the hepatic artery. He states that after ligation of the hepatic artery above and below the aneurysm, the latter bled pro-
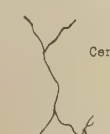
7. Tuffier: Presse méd. **17**:153, 1909; Allessadria: Bol. Acad. de med. de Roma, **32**:63-67, 1906.
8. Kehr: München. med. Wchnschr. **1**:1861-1867, 1903.

fusely after it was opened, necessitating a tight tamponade. Kehr concluded from this observation that ligation of the hepatic artery was the proper treatment. Baruch dissents from this opinion on account of the occurrence of experimental necrosis following the ligation of the hepatic artery in animals.

TABLE 4.—Sites of Ligation and Results Obtained After Operation on the Hepatic Artery of the Dog

Dog	Site of Ligation	Death Following Operation	Death by Chloroform	Liver Changes	
				Gross	Microscopic
1	Central		33 days	Paling of portion of under surface of liver	(No sections made)
2	Central		38 days	No changes noted except for adhesions in gastrohepatic region	Portal veins dilated; organizing thrombi in some vessels; liver cells swollen and fine vacuoles present; yellow, amorphous pigment present
3	Central		35 days	None noted, except dense adhesions about gastrohepatic region	(No sections taken)
4	Central	4 days from sepsis		Appears normal except for few small areas of gray coloration	Capsule normal; central zone of each lobule shows destruction of liver cells and replacement by cellular detritus red blood cells, and amorphous pigment; large bacilli scattered throughout detritus
5	Central and Peripheral		113 days	Liver of normal consistency and color; very few adhesions	Liver cells are swollen, pale, and filled with fine vacuoles; nucleus absent in many instances; yellowish, amorphous pigment in abundance; portal veins not dilated

Narath has collected all the articles on ligation of the hepatic artery, particularly the work of von Haberer. The data disclose that the vitality of the liver depends on the site of the ligation. The more centrally the ligature is placed, the greater the chance of recovery. The results also show that ligation of a branch of the hepatic artery in most cases resulted in the death of the animal from hepatic necrosis.

If death does not follow, the necrotic area is encapsulated. All this is in conformity with our own experimental work. In addition, we found that one or two animals survived because of adhesions of the liver to the diaphragm and of the great omentum to the parietal peritoneum, forming, so to speak, an accessory anastomosis similar to that following a
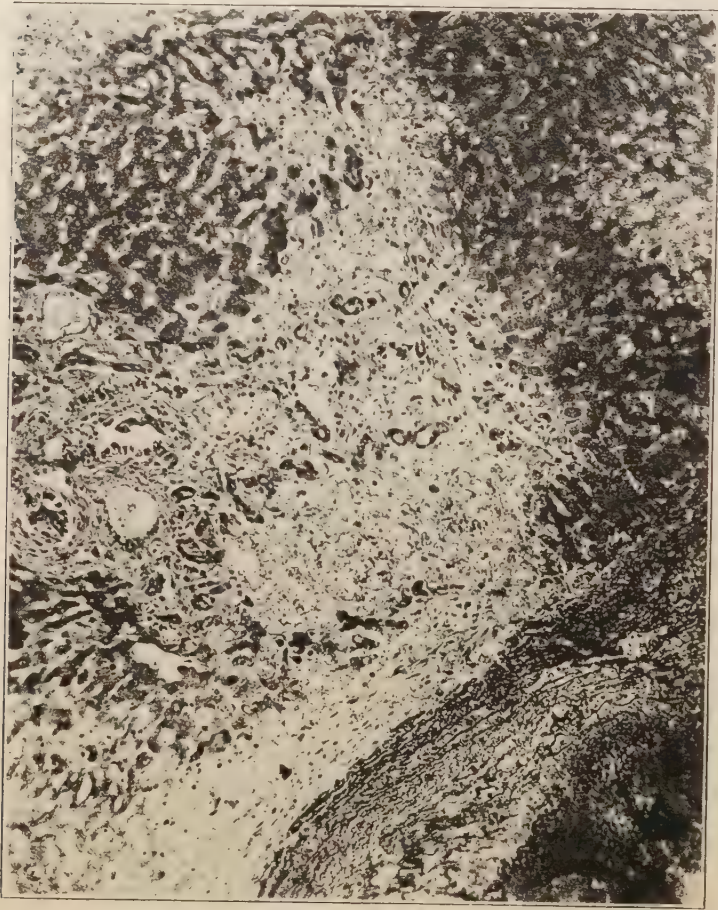
Fig. 11.—Same as Figure 10, but showing a lesser degree of degeneration (Radasch).
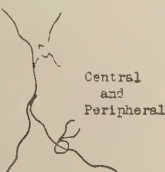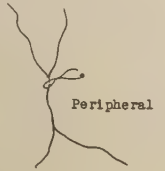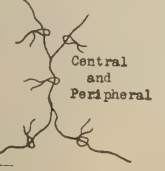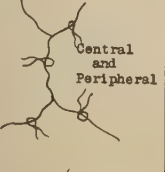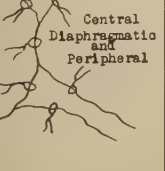
Talma operation for cirrhosis of the liver. The occurrence was so striking that our attention was directed to this phenomenon.

TECHNIC

Prior to operation all animals were shaved, tincture of iodin was applied to the skin, and then the field of operation was surrounded with a sterile sheet. The instruments were boiled between operations, when more than one was per-

formed on the same day. The hands were thoroughly scrubbed. Gloves were not used. Ether anesthesia was used altogether, except in the case of cats, when chloroform was employed to induce stupor only, after which ether was given. Chloroform was tried on dogs, but they were so susceptible to it

TABLE 5. — Sites of Ligation and Results Obtained After Operation on the Hepatic Artery of the Cat

Cat	Site of Ligation	Death Following Operation	Death by Chloroform	Liver Changes	
				Gross	Microscopic
1	Central and Peripheral		23 days	No changes noted	(No sections made)
2	Peripheral		23 days	No changes noted	(No sections made)
3	Central and Peripheral		20 days	Liver shows no gross change; gallbladder thickened and tough; adhesions	Hydropic degeneration of liver cells; immediate subcapsular region is congested; some central veins contain coagulum; portal veins dilated
4	Central and Peripheral		19 days	Dense adhesions in region of gallbladder; no other changes noted	Capsule normal; central veins congested; liver cells generally show hydropic degeneration, but are best preserved in subcapsular areas
5	Central Diaphragmatic and Peripheral	48 hours		Soft, succulent, and paler in some areas than in others	Universal necrosis

that we were compelled to use ether exclusively. Silk was used in all ligation; the wounds were closed with catgut and silk sutures. A pad was always placed at the border of the ribs posteriorly so as to render the structures around the foramen of Winslow nearer to the field of operation.

MORPHOLOGIC AND HISTOLOGIC REPORT

The following morphologic and histologic report by one of us (Dr. Radasch) describes the results of our experimental work mentioned in the preliminary note. In the main, these descriptions were confirmed in our final experiments.

The necropsy of one of the rabbits that died between four and five days after ligation showed that the liver had undergone serious changes. Between
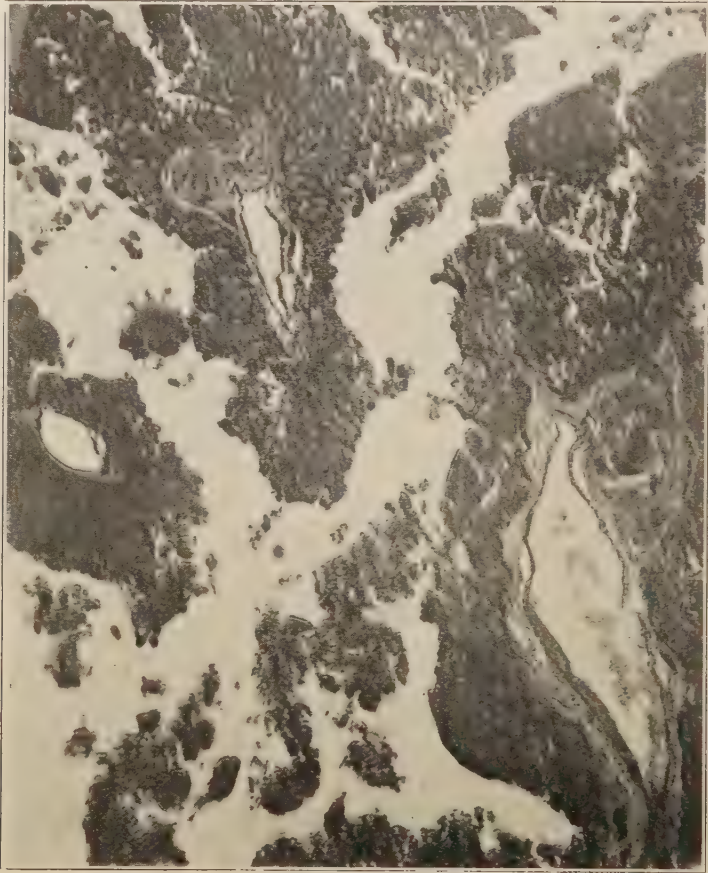
Fig. 12.—Parenchymatous degeneration; portal canals unusually prominent (Radasch).
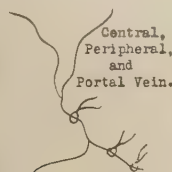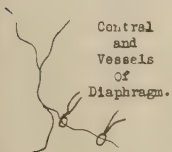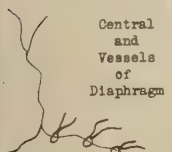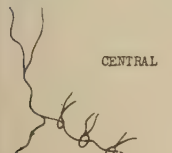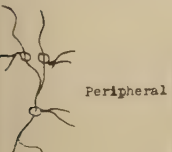
the right lobe and the diaphragm, there was a layer of light yellow material that seemed to be necrotic liver tissue. The left lobe of the liver was mottled with reddish and whitish patches. The cardiac part of the stomach also showed a yellowish patch.

The surface of sections showed a thick layer of granular material which under the higher power was seen to consist of many leukocytes (chiefly polymorphonuclear cells and some lymphocytes) and necrotic substance. In

some areas, the cells predominated and in others the granular necrotic material was predominant. Separating this necrotic layer from the liver cells was the scarcely perceptible capsule of the liver. In places the capsule seemed absent and the liver cells underneath had undergone a degenerative change in varying degrees; some were entirely destroyed, while others were very nearly so, or showed only early changes. Many areas of focal necrosis were noticeable and

TABLE 6. — SITES OF LIGATION AND RESULTS OBTAINED AFTER OPERATION ON THE HEPATIC ARTERY OF THE CAT

Cat	Site of Ligation	Death Following Operation	Death by Chloroform	Liver Changes	
				Gross	Microscopic
6	Central, Peripheral, and Portal Vein.	18 hours		Pale, soft and flabby	Total necrosis
7	Central and Vessels of Diaphragm.		14 days	Many adhesions; two lobes of liver a degree paler than normal	Portal veins injected; central veins distended; hydropic degeneration of liver cells; no massive necrosis
8	Central and Vessels of Diaphragm		63 days	Many adhesions; liver considerably paler than normal; no change in consistency	Irregular focal necrosis in central parts of lobules; hydropic degeneration of cells toward periphery of lobule; some enlargement of all the vessels
9	CENTRAL		40 days	Liver much paler than normal; gallbladder apparently normal; inferior surface of liver shows small, pale, raised areas	Cells swollen and pale; certain areas contain irregular, clear vacuoles; nuclei generally pale, and some entirely missing (hydropic degeneration)
10	Peripheral		27 days	Adhesions but no other changes	(No sections made)

some of these were quite large and chiefly subcapsular. The hepatic cells in general exhibited parenchymatous changes, especially the nuclei. The latter responded very poorly to the stain. Some of the larger biliary ducts showed changes. The epithelium was partly desquamated and the remainder showed cloudy swellings (Figs. 10 and 11).

Another section of liver from a rabbit that lived five days after the operation showed a somewhat thickened capsule and the cells showed proliferation on the deeper surface. The hepatic cells in general showed parenchymatous degeneration to a marked degree. There were a few small necrotic areas, and small groups of round cells were noted. The cell chains were very much attenuated in places, and the cells showed atrophy. The portal canals were unusually prominent (Fig. 12).
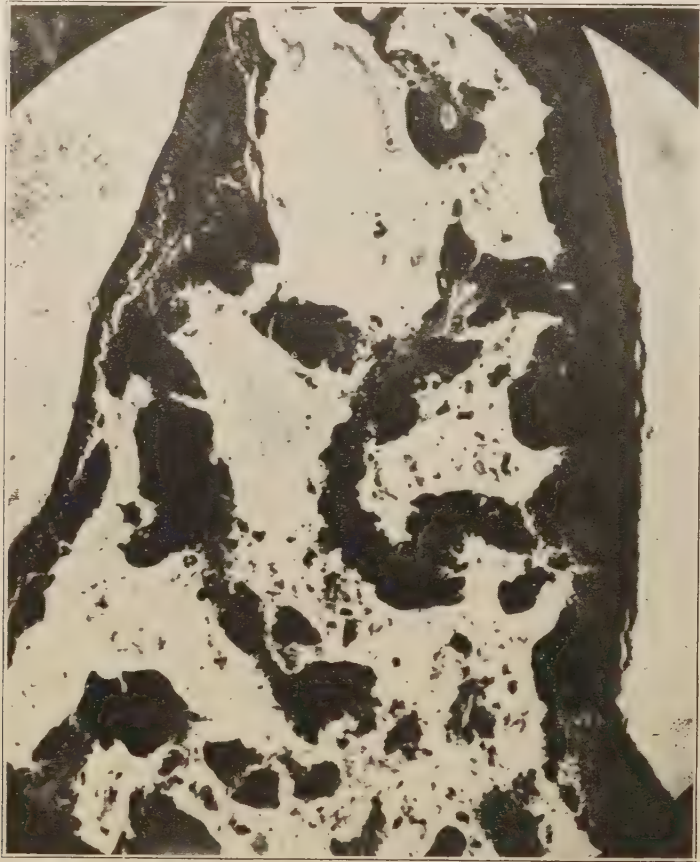
Fig. 13.—Most extensive changes. The liver in fresh state showed many small holes (Radasch).

Another section exhibited the most extensive changes so far studied. Even in the fresh state (at removal), the liver showed many small cavities that communicated with one another. In section this condition was emphasized and gave the appearance of having been riddled with shot. The same section represented the thin margin of the liver, and with the unaided eye the numerous small spaces left by the removal of the necrotic tissue gave characteristic appearance to the section. The capsule showed very little thickening, and the mesothelium for the most part was absent. Most of the remaining hepatic epithelium showed marked parenchymatous degeneration. A few cells gave

a good nuclear stain, but these cells were mostly small and atrophic with enlarged sinusoids between them. The portal canals all stood out prominently and in some of these areas the branches of the bile ducts showed desquamation of the epithelium. In the interlobular tissue of the portal canals an unusually large number of thin walled blood vessels of considerable caliber may be noted (Fig. 14).

Conclusions.—(Dr. Radasch).—The lesion resembles somewhat the changes that occur in acute yellow atrophy of the liver. The diminution in size is not so marked, but the mottling is apparent.

While the microscopic changes in acute yellow atrophy usually show fatty degeneration and the presence of fat droplets and hyaline material, in the section studied there seemed to be an absence of fatty material of all kinds. The cells have undergone a rapid parenchymatous and necrotic change so that the architecture is destroyed and there remains only an amorphous mass of granular necrotic material. The term "necrobiosis" seems well chosen to express the condition, as a "living death" seems to be exemplified in the shrinking and degenerating cells.

This result of ligation of the artery seems to indicate an acute anemia of the liver. The hepatic vessel is far too small a vessel to act as the nutrient vessel of the organ, that is the function of supplying the liver with food.

The liver is an important oxidizing organ. The various toxins formed by the putrefaction of proteins in the intestines are brought to the liver by the portal vein, and through the action of the liver cells, these substances are oxidized and rendered harmless substances that the kidneys later eliminate. If the liver cells are deprived of this and other oxygen, they cannot perform these chemical changes, and also degenerate as the result of the presence of these toxins and the inability to repair their own wear and tear.

It would appear that any injury which prevents the proper amount of oxygenated blood from getting into the liver gives rise to an acute anemia that is followed by general necrobiosis of the hepatic tissue.

GENERAL CONCLUSIONS

Ligation of the hepatic artery is dangerous at all times. This has been proved in the few cases reported in which a deliberate ligation in man was one of necessity on account of aneurysm or other pathologic conditions. (Only one patient recovered [Kehr's].)

There is a varying susceptibility of animals to the effects of ligation of the hepatic artery. This depends on the point of ligation to a certain extent, namely, whether the ligation is made centrally or peripherally.

Rabbits and guinea-pigs always succumb to successful peripheral ligation. Dogs and cats resist the ligation and continue to live indefinitely in spite of a combination of a peripheral and central ligation.

An important point to be kept in mind is that histologically we have found degeneration of the liver cells in all animals in which ligation was performed.

STUDIES ON EXPERIMENTAL PLETHORA IN DOGS AND RABBITS.*†

BY EDWARD B. KRUMBHAAR, M.D., PH.D., AND ALFRED CHANUTIN, PH.B.

(*From the John Herr Musser Department of Research Medicine of the University of Pennsylvania and the Laboratories of the Philadelphia General Hospital, Philadelphia.*)

The object of the present communication is to present the functional changes produced by repeated transfusions in the blood-making and blood-destroying apparatus and in metabolism, and also the structural changes in the viscera of dogs and rabbits. The source of an anemia that developed during the plethoric stage has also been considered. In an attempt to throw further light on the relation of the spleen to blood formation and blood destruction, we first studied the effect of splenectomy in artificial plethora, and tried to find evidence of increased enzyme action in the spleen removed at a time when blood was being destroyed in greatly increased quantities. Not only were these efforts barren of results, but it was also found that our knowledge of the changes caused by the artificial induction of plethora was in itself meager.

I.

Blood Formation and Destruction.

A few writers have studied the effect of plethora on rabbits, animals notoriously inconstant in their hemopoietic reactions. Hess (1) induced plethora in rabbits by repeated transfusions in order to study the effect on the work of the heart, and Itami (2) studied the tissue changes in these same animals. These writers also described an extremely plethoric rabbit, which, in spite of continued transfusions and of the absence of isolysins, developed a marked anemia. Robertson (3) has described more thoroughly this type of plethoric anemia and has shown

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the relationship of plethora and anemia to bone marrow activity, as indicated by the percentage of reticulated red cells. This writer found that agglutinins developed coincidentally with the anemia, but did not give quantitative details of the results. Kambe and Komiya (4) also encountered this anemia in rabbits that had been made plethoric and also demonstrated the presence of agglutinins qualitatively.

Ottenberg and Thalhimer (5) found that isohemolysins are seldom present in the blood of normal cats, but that they often appear in the blood of recipient cats after transfusions. With the development of hemolysins, the animals developed a marked anemia, from which they quickly recovered after cessation of transfusions. Ottenberg, Kaliski, and Friedman (6) demonstrated the presence of isoagglutinins and isohemolysins in dogs. These authors also showed that direct transfusion of blood that is agglutinated and laked by the recipient's blood is followed by the destruction of the transfused blood with an intense intoxication. Boycott and Douglas (7, 8) observed that dogs do not destroy cells during the days immediately following a first transfusion, but that once the animal has become accustomed to destroying blood, it can dispose of the transfused red blood cells two to eight times as fast as after the first transfusion. They therefore think that some mechanism must be developed by the animal for the rapid destruction of foreign red cells. Since Boycott and Douglas could find no evidence of isohemolysins after the transfusions, they concluded that transfused red cells were not destroyed by direct hemolysis.

Methods.

Plethora was produced in dogs by daily transfusions of 25 to 200 cc. of whole blood taken from six compatible donors in rotation. Dogs weighing from 6 to 10 kilos were used as recipients and larger animals as donors. With careful technique the jugular veins were used during the entire experiment for aspiration of blood from the donor and injection into the recipient. The donor's blood was drawn into an Erlenmeyer flask containing 2 cc. of 10 per cent sodium citrate for every 100 cc. of blood, to prevent clotting. The blood was allowed to flow into the recipient from a sterile burette by gravity. The hemoglobin and the total blood volume figures were used for estimating the degree of plethora.

Hemoglobin was determined by the Newcomer (9) method, and the vital red method of Keith, Rowntree, and Geraghty (10) was used in the estimation of the blood volume. The method of Wilbur and Addis (11) was employed for the determination of urobilin as an index of blood destruction.

Bone marrow activity was studied by estimating the percentage of reticulated or "skeined" erythrocytes. It is suggested that for the sake of brevity, the word "reticulocyte" be substituted for "reticulated erythrocyte," and the term "reticulosis" be designated to replace some such expression as "an increase in the number of reticulated cells," as is now the custom. The percentage of reticulocytes was estimated after vital staining with Grübler's brilliant cresyl blue.[1] The recipients were fed a standard diet of beef heart, cracker meal, sugar, lard, bone ash, and salt, and the donors were given table scraps. The test animals gained in weight during the experiment, while the donors became only slightly anemic with only a small rise in the percentage of reticulocytes. Removal of the spleen was performed under ether anesthesia without noteworthy loss of blood.

RESULTS.

Production of Plethora.

Seven dogs were rendered plethoric by the method described. The degree of plethora obtained did not depend on the amount of blood injected; for instance, one dog given twenty transfusions, averaging 48 cc., attained as great a rise in hemoglobin as another injected twenty-three times, each transfusion averaging 157 cc. The largest number of transfusions in one animal was 61 in 76 days; the shortest period was 15 days with eleven transfusions in a fatal case. The maximum hemoglobin obtained in these plethoric animals varied from 146 to 226 per cent (Text-figs. 1 to 4).

A peculiar result was noted in three out of four dogs (Nos. 1, 2, and 3) when transfusions were discontinued during the height of plethora; namely, a temporary rise in hemoglobin of 11, 17, and 21 per cent, occurring on the 3 following days. This was also noted by Boycott and Douglas in one of their rabbits. The drop in hemoglobin after the sudden rise was almost as striking. The fourth dog (No. 4) maintained a constant hemoglobin level for 10 days before the transfusions were stopped, and upon ceasing injections, there was a sudden drop. It is suggested that possibly some organ, such as the liver, acts as a blood storehouse, and upon cessation of transfusion, a further rise in

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[1] American preparations of this stain have not been of any use in our hands.

blood count is caused by excess blood being thrown into the blood stream.

The results of our investigations have shown that the excess blood is destroyed as rapidly by the splenectomized as by the normal dogs, after ceasing the transfusions. Three dogs were made plethoric, their spleens removed, and transfusions stopped; the fourth dog used for a control was made plethoric but was not splenectomized. In all four cases, after discontinuing transfusions, the blood was destroyed with approximately equal rapidity, as indicated by hemoglobin and blood volume studies. After 4 to 6 weeks the hemoglobin had returned to normal and then a moderate anemia (hemoglobin varying from 15 to 27 per cent below normal) persisted for a few weeks, followed by a permanent return to normal. This anemia might be considered as an expression either of the time required by the bone marrow to recover from its enforced inactivity, or more probably of the organism's attempt to rid itself of its newly acquired powers of increased blood destruction.

The first few transfusions raise the hemoglobin percentage only very slightly. The reactions of animals during this time differ widely. Dog 3, for example, was transfused with 620 cc. of blood in 4 days, causing the hemoglobin to rise from the normal of 86 per cent to only 98 per cent. Another dog's (No. 2) hemoglobin increased only 9 per cent by the 3rd day after 95 cc. of blood had been transfused. The organism can apparently handle this excess blood during the first few days of transfusions without showing any signs of marked increased blood destruction, as will be shown below in the urobilin and metabolism studies.

One apparently successful attempt was made to break down an animal's blood-destroying mechanism (No. 5) by transfusing relatively massive quantities of blood (averaging 133 cc. per day). It was possible, by this means, to obtain a rise in hemoglobin from 98 per cent to 200 per cent in 11 days. With the continuance of these large daily transfusions, however, this very high blood concentration was after 8 days reduced by the organism to 150 per cent. Continued transfusions then apparently killed the animal after a second rise in hemoglobin to 226 per cent. The red cell count, at this time, was 15,500,000, as compared with the normal of 7,160,000. The cause of death of this animal will be considered later.

Anemia Following Plethora.

This anemia, developing in spite of and probably on account of continued transfusions, is characterized by a marked fall in hemoglobin and red blood cells with at first little reticulocyte evidence of regeneration. In one splenectomized dog (No. 6, Text-fig. 1), the anemia developed rapidly until, at the end of 15 days, the hemoglobin had fallen from 138 per cent to 21 per cent; there was then a temporary rise for several days, followed by a fall to 13 per cent, when it reached the point of greatest severity. Although transfusions were continued daily at this time, the hemoglobin at the end of 13 days was 17 per cent. The injections were stopped and the hemoglobin returned to normal slowly. In another animal (No. 7, Text-fig. 3), in which transfusions were continued after splenectomy, the hemoglobin fell from 185 per cent to 67 per cent during a period of 18 days; with continued transfusions, however, the hemoglobin rose again to a high figure.

The experiment with Dog 6 was controlled by transfusing equal amounts of blood from the same donors into a normal dog (No. 4). This animal developed an artificial plethora (which persisted until transfusions were discontinued) without anemia (Text-fig. 2). The significance of this disparity will be discussed later.

Bone Marrow Activity in Plethora and Anemia.

Our experiments with dogs have confirmed Robertson's (3) findings in rabbits that reticulocytes practically vanished during the stage of artificial plethora, but were greatly increased during the "plethoric anemia" stage (Text-figs. 1 to 4). The value of reticulocytes as an index of bone marrow activity and blood formation is especially evident in Text-fig. 1, which shows the sudden anemia following plethora in Dog 6. The sudden fall in hemoglobin is seen to be accompanied by a slight increase in reticulocytes, which had been practically absent in the plethoric stage. This reticulosis became marked after the anemia had been in progress 2 weeks, and after transfusions had been stopped, the reticulocytes increased to the extremely high level of 81 per cent. The animal's hemoglobin and reticulocytes gradually returned to normal after transfusions
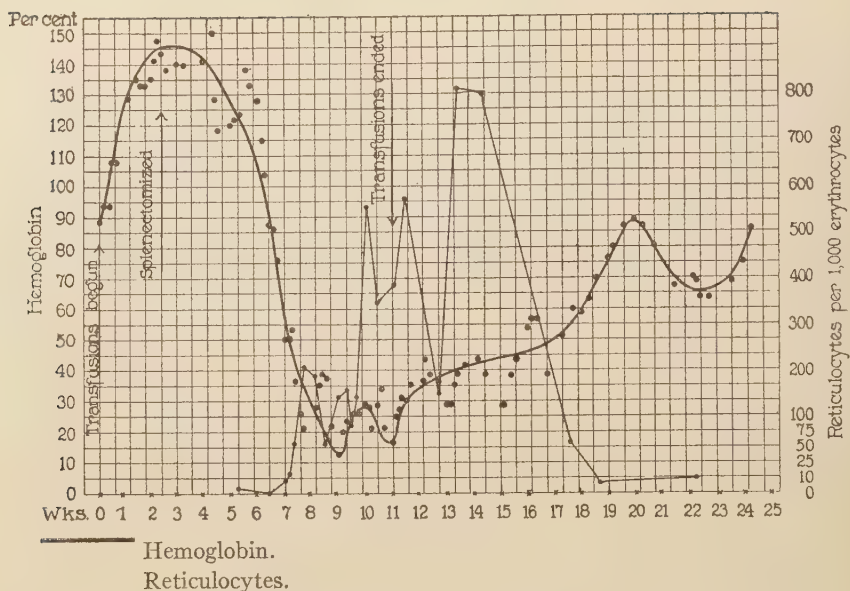
TEXT-FIG. 1. Dog 6. Reticulocyte and hemoglobin curves in experimental plethora and "plethoric anemia." The amount of blood transfused was 5,965 cc.
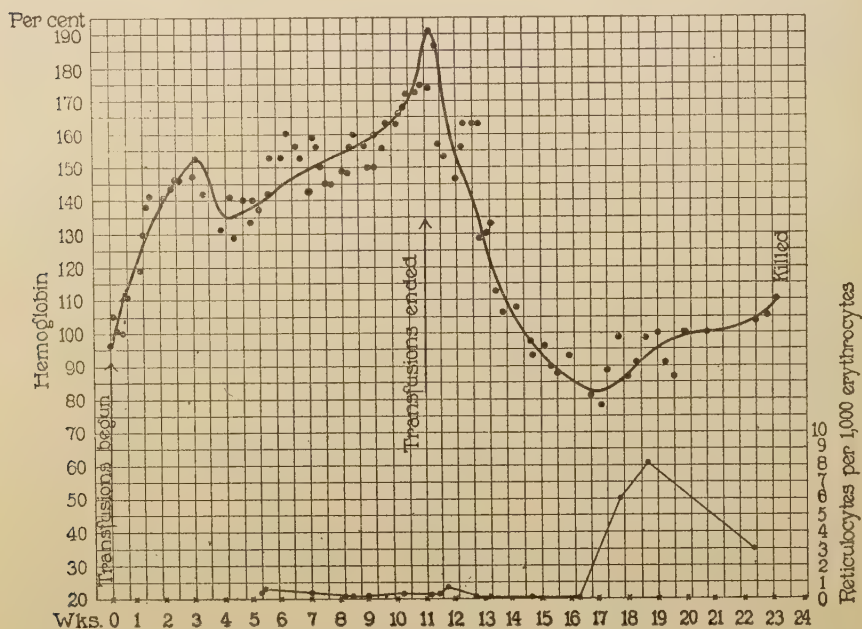
TEXT-FIG. 2. Dog 4. Reticulocyte and hemoglobin curves in experimental plethora. The amount of blood transfused was 6,150 cc.
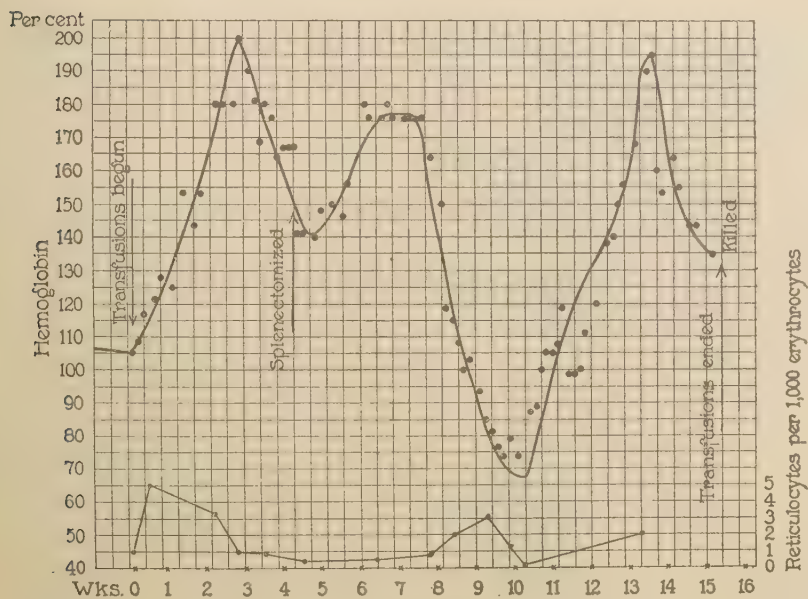
TEXT-FIG. 3. Dog 7. Reticulocyte and hemoglobin curves in experimental plethora and "plethoric anemia." The amount of blood transfused was 10,450 cc.
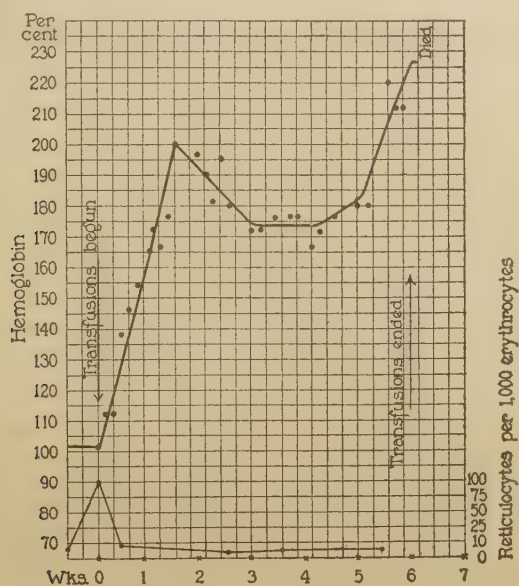
TEXT-FIG. 4. Dog 5. Reticulocyte and hemoglobin curves in fatal experimental plethora. The amount of blood transfused was 5,000 cc.

had been discontinued. In Dog 7, in which a slight anemia developed after splenectomy, the slight increase in reticulocytes should be noted in passing.

Blood Volume Studies.

The vital red method of Keith, Rowntree, and Geraghty gives, according to Smith, Arnold, and Whipple (12), an accurate index of plasma volume, but is less reliable for red cell volume determinations. One can, however, obtain comparable results when working on the same animal for a long period of time. Keith, Rowntree, and Geraghty (10) observed in many anemic patients an increase of plasma volume and found that in polycythemia the plasma volume may be either low or high—in the latter case true plethora may be said to exist. Bock (13), on the other hand, studying the blood volume in pernicious anemia, has shown that as long as the hemoglobin remains above 30 per cent, there is a remarkable constancy of plasma volume. In patients with lower hemoglobin, there is a corresponding reduction of the plasma volume. The variations in blood volume are, for the most part, due to changes in red cell content. Denny (14) also finds that the plasma volume is essentially normal in pernicious anemia, and a decrease in total volume is due to loss of cell mass. The constancy of the plasma volume is also shown by Peters and Rubnitz's (15) report that the plasma nitrogen has no tendency to decrease in anemia.

In four dogs studied, the total blood volume was, as might be expected, greatly increased above normal in the plethoric stage and decreased below normal in the anemic stage (Tables I to IV). With the exception of one animal (No. 5), which died from the induced plethora, the plasma volume showed surprisingly few changes, either in anemia or plethora. The changes in red cell volume were chiefly responsible for the variations in total blood volume, so that the plethora might properly be termed "acythemic plethora."

It is interesting to note, in agreement with Bock's and Denny's findings, that in the extreme anemia obtained in Dog 6, the total red cell volume was estimated, once at 55 cc. and 5 days later at 37 cc., while the plasma volume remained practically normal. The total blood volume dropped from a normal of 980 cc. to a minimum of 512 cc. The anemia in Dog 7 was manifested by a change from the normal blood volume of 1,000 cc. to 794 cc. The plasma volume in this dog during the anemic period was identical with the normal, with a diminished red cell volume.

With extreme plethora (No. 5) there was a marked diminution in plasma volume, together with an increased red cell volume. This diminution of plasma volume is present to a slight extent in all cases of extreme plethora during the early stages of transfusions. There is then manifested a tendency for the plasma volume to return to the original level.

Urobilin Excretion.

The amount of urobilinogen and urobilin in the urine and stools is now generally recognized to be a fairly accurate index of the degree of blood destruction in the body (Wilbur and Addis (11) and Robertson (16)). As the experimental animals were on a constant diet throughout the experiments, Whipple's (17) demonstration that bile pigment elimination can be greatly changed by modification of diet does not apply to these experiments.

Urobilin was found to be present in the urine in small amounts only during periods of marked blood destruction. Urobilin determinations were made on the feces of three dogs (Nos. 4, 6, and 7), the first two of these having received equal amounts of blood from the same donors. Dog 4 reached a maximum urobilin excretion of 8,000 units at the same time that the plethora reached its maximum. At this point transfusions were stopped, and both blood count and urobilin excretion returned gradually to normal. Dog 6 showed a maximum output of 14,400 units at the height of the "plethoric anemia." This high urobilin output continued for about 4 weeks. When transfusions ended, and the dog's hemoglobin began to rise, accompanied by a simultaneous reticulosis, the urobilin excretion was greatly diminished. Dog 7 also showed a greatly increased urobilin elimination but press of work did not permit many determinations at this time. (Tables I to III.)

Blood Counts.

Hemoglobin and erythrocyte determinations have already been considered. Leucocytes, estimated during the course of the experiments, were considerably increased, chiefly due to an increase of polymorphonuclear leucocytes; but changes were so inconstant and unexplainable that they will not be further considered. Fragility

tests made on several animals during the course of the experiments showed an increase in both the maximum and minimum resistance, both during the plethoric and anemic stages, but these were not

TABLE I.

Blood Changes in Experimental Plethora and "Plethoric Anemia."
Dog 6.

Length of time after first transfusion.	Hemo-globin.	Red blood cells.	Plasma volume.	Red cell volume.	Total blood volume.	Urobilin units.	Remarks.
days	per cent	millions	cc.	cc.	cc.		
(Normal.)	87		545	435	980	400	Mar. 9, 1920. Transfusions begun.
5	116		580	640	1,220	600	
8	128		645	925	1,570		
14	135		515	1,095	1,610	1,920	Splenectomized.
21	140		445	865	1,310		
23	140		427	905	1,332		
35	120		512	798	1,310		
37	123		475	775	1,250		
40	133		520	780	1,300		
45	87	4.6	583	373	956	2,400	
49	50	3.5	590	175	765		
51	53	2.5	560	115	675	11,200	
53	26	1.8	607	54	661		
57	27	1.2	640	70	710		
63	13	0.65	580	55	635	14,400	
68	26	1.39	475	37	512	13,000	Injections ended.
77	17	1.71				11,300	
78	25	1.55					
95	39	1.97	437	110	547		
102	39	2.6				3,120	
112	57	2.88	535	230	765		
122	52	3.1	550	194	744		
127	59	3.8	568	210	778	640	
158	64	3.68	568	190	758		
166	69		578	272	850		
171	87		510	300	810		
215	82	5.6					

5,965 cc. of blood transfused in 60 injections; average 99 cc. per transfusion.

sufficiently striking or constant to be given in detail. Except for the slight increase in resistance of the slightly anemic donor's cells, it is difficult to see why such a change in the fragility of the blood of

the experimental animals should have taken place during plethora. A possible explanation would be that with the increased need for

TABLE II.

Blood Changes in Experimental Plethora.
Dog 4.

Length of time after first transfusion.	Hemo-globin.	Red blood cells.	Plasma volume.	Red cell volume.	Total blood volume.	Urobili units.	Remarks.
days	*per cent*	*millions*	*cc.*	*cc.*	*cc.*		
(Normal.)	105		580	448	1,028	300	Mar. 9, 1920. Transfusions begun.
7	111		540	880	1,420	1,200	
14	141					1,500	
20	146		508	966	1,474		
22	153		465	825	1,290		
33	140		460	860	1,320		
42	153		378	806	1,184		
44	160		380	810	1,190	2,340	
46	156		525	805	1,330		
49	144		562	1,000	1,562		
51	156	10.9				4,400	
53	140		535	995	1,530		
57	144	11.8				1,800	
63	156	12.8	440	935	1,375	5,400	
72	168	12.7	342	928	1,270	1,870	
77	174					3,230	
78	174	12.7					Injections ended.
80	181	13.8				8,000	
100	108	12.8	515	515	1,030		
104	93	7.4				2,400	
110	88	7.0	565	425	990		
122	88		537	253	790		
127	81	6.6	515	302	817		
132	98	7.4				2,160	
158	105	6.6	592	468	1,060		
163	110					720	Killed.

6,150 cc. of blood transfused in 59 injections; average 104 cc. per transfusion.

blood destruction, the more fragile cells from each transfusion were soon destroyed, leaving the average of those remaining higher than normal.

TABLE III.

Blood Changes in Experimental Plethora and "Plethoric Anemia."
Dog 7.

Length of time after first transfusion.	Hemo-globin.	Red blood cells.	Plasma volume.	Red cell volume.	Total blood volume.	Urobilin units.	Remarks.
days	*per cent*	*millions*	*cc.*	*cc.*	*cc.*		
(Normal.)	105	6.84	550	450	1,000	400	May 17, 1920. Transfusions begun.
5	121	7.9	612	638	1,250		
9		9.1				900	
24	168	12.4	460	1,840	2,300		Splenectomized.
30	167	12.4	392	1,298	1,690		
39	146	10.7	342	948	1,290		
44	176		432	1,168	1,600		
51	176	11.6	545	1,475	2,020		
58	117	7.4	460	500	960		
65	85	5.8	560	300	860		
71	74	5.1	555	239	794		
80	98		527	448	975		
87	138	7.5	510	622	1,132		
95	195		512	1,088	1,600	4,000	
100	155		440	935	1,375		Killed.

10,450 cc. of blood transfused in 88 injections; average 118 cc. per transfusion.

TABLE IV.

Blood Changes in Fatal Experimental Plethora.
Dog 5.

Length of time after first transfusion.	Hemo-globin.	Red blood cells.	Plasma volume.	Red cell volume.	Total blood volume.	Remarks.
days	*per cent*	*millions*	*cc.*	*cc.*	*cc.*	
(Normal.)	98	7.16	364	411	775	May 25, 1920. Transfusions begun.
1	102	8.12				
2	112					
4	138	9.16				
8	172	11.2				
12	200	12.8				
18	180	14.4	325	1,295	1,620	
24	172	15.2				
30	172		174	792	966(?)	
40	220	15.5	212	1,418	1,630	Death 4 days later.

5,000 cc. of blood transfused in 39 injections; average 133 cc. per transfusion.

II.

Metabolism Studies.

Although early in our work we devoted our attention solely to urobilin excretion, it later seemed advisable to study the influence of the artificial plethora and its consequent anemia on the nitrogenous metabolism, in the presence of daily parenteral introduction of large amounts of isoprotein.

The dogs used for each experiment were placed in metabolism cages, on a constant diet of raw beef heart, cracker meal, sugar, lard, bone ash, and sodium chloride, that had a known, sufficient caloric value. Water was given *ad libitum*. After 1 or 2 weeks on this special diet, if the weight of the animal remained constant, a preliminary metabolism study was made; Dogs 4 and 6 were first studied metabolically after the transfusion experiments were well in progress. The constant diet was continued between periods of metabolism study, so that although the introduced nitrogen was not actually determined, changes in elimination can reasonably be attributed to the transfused blood. Each dog was catheterized at the end of 24 hours, with the exception of one male (No. 6) chosen before the metabolic studies were contemplated. Although this renders the 24 hour periods less precise than those of the females, the length of the series studied prevents gross error in this particular experiment, if averages of several days are considered. None of the animals showed loss of weight or other ill effects during the period of metabolic study, except one (No. 5) which on account of anorexia and diarrhea could not be included in this study.

In the analysis of the urine, the total nitrogen was determined by the Kjeldahl-Gunning method, urea by Folin's aeration method, ammonia by the procedure of Van Slyke and Cullen, creatinine and creatine by Folin's method, uric acid by the Hotchkiss-Benedict modification, and total phosphates by the uranium acetate method.

Forster (18, 19) demonstrated many years ago that whole dog blood transfused into a dog in moderate amounts had a marked stability, since he failed to obtain an appreciable rise in the nitrogen output. On the other hand, foreign serum injected in the same manner is destroyed more as though given *per os*. Tschiriew (20), confirming the experiments of Forster, found that dog blood introduced by

mouth is completely metabolized in contrast to an equal amount of "living" dog blood, which may be given intravenously with little or no increase in nitrogen excretion. From these experiments, we must conclude that transfused blood protein is not immediately destroyed and that its protein is utilized when given as a food.

The nitrogenous metabolism of Dog 7 is presented (Table V) as an example of the changes that occur before and during the plethoric and anemic stages. Although the nitrogen intake in food and blood transfusions was not determined, the results of nitrogen output are

TABLE V.

Nitrogen Metabolism in Experimental Plethora.

Length of time after first transfusion.	Weight.	Volume.	Specific gravity.	Urine per day.							Feces per day.
				Total N.	NH₃ N	Urea N.	Creatinine.	Creatine.	P₂O₇	Uric acid.	N
	kg.	cc.		gm.	gm.	gm.	mg.	mg.	mg.	mg.	gm.
Normal (5 day period)	9.19	555	1,014	4.31	0.30	3.33	328	181	309	59	0.65
3rd and 4th days (2 day period)...	9.13	635	1,013	4.28	0.26	3.34	262	233	189	54	
8th to 13th day (6 day period)...	9.37	585	1,015	4.89	0.30	3.80	291	208	255	63	0.62
24th " 29th " (6 " ")...	9.50	740	1,011	5.28	0.32	4.31	314	121	273	69	0.46
Splenectomized on 30th day.											
31st to 35th day (5 day period)...	9.14	592	1,016	6.98	0.31	5.82	338	172	377	55	0.50
47th " 51st " (5 " ")...	9.26	538	1,013	7.08	0.30	6.07	307	225	302	85	0.40
58th " 63rd " (6 " ")...	9.10	478	1,018	7.31	0.31	6.28	279	143	352	72	
66th " 70th " (5 " ")...	9.03	400	1,017	6.07	0.31	5.11	251	117	282	59	
73rd " 81st " (9 " ")...	9.27	502	1,014	6.33	0.28	5.17	299	143	299	85	

so striking that certain conclusions can, nevertheless, be drawn. In Dog 7 during the first 10 days of the experiments, 1,200 cc. of blood were transfused, representing roughly 36 gm. of nitrogen. The nitrogen output in urine and feces for this period was practically normal, indicating that the nitrogen in excess of that accounted for by the plethoric vascular system was being stored by the body. With continued transfusions, the nitrogen output rose, but never commensurately with the amount injected. With the onset of anemia, the nitrogen excretion rose to its highest point; but during the course of the anemia, there was no such marked nitrogenous excretion.

Dog 4 was first studied metabolically while the hemoglobin was returning to normal after transfusions had been stopped. The first period, during plethora, showed a high nitrogen output; when a decrease in blood volume had occurred, the nitrogen excretion was practically normal as judged by the food intake.

In Dog 6 metabolism studies were first done while transfusions were being made, during the period of anemia. A relatively high nitrogen output was found, which decreased to about normal soon after the transfusions were stopped. During the period of recovery, there was a much lower excretion of nitrogen, which appears to be lower than normal. It is problematic at what stage the excess nitrogen of transfused blood is excreted, since there is apparently no indication from these analyses that excess, or even equal amounts of nitrogen are excreted at any time except previous to sudden development of anemia. Albumin was occasionally present in the urine during extreme plethora and at the beginning of anemia, but never in quantities that would account for the nitrogen introduced.

The creatinine, creatine, and phosphate studies give no noteworthy information about the processes concerned in blood destruction. The urea excretions paralleled the total nitrogen, but the ammonia excretion was apparently not affected. The feces nitrogen was relatively constant. It was thought that the cell destruction would be so great that a study of uric acid metabolism might be of interest, even though allantoin determinations were not made. The result, however, showed no constant or marked changes.

In the urine of all animals made extremely plethoric, bile and albumin could be detected in appreciable amounts. This was also noted during the period of anemia.

<div style="text-align:center">III.</div>

Postmortem Findings.

By far the most striking change in the organs of our plethoric animals is the tremendous deposition of hemosiderin in the spleen, liver, lymph nodes, and bone marrow. Its almost complete absence from other organs is strong evidence of the important part that these organs play in the storage and elimination of the products of increased

blood destruction. Its absence from the kidney accords with the absence of hematuria or hemoglobinuria, though differing from various experimental and clinical conditions in which pigment deposition has been marked in this organ.

In animals killed or dying while transfusions were being continued, there is also, as would be expected, extreme congestion of blood vessels throughout the body. This is so marked in the viscera that details of structure often are obscured, so that it is usually impossible, for instance, to determine whether given groups of cells are packed into phagocytes or into small vessels. It is safe to say, however, that pigment phagocytosis either entirely replaces or at least is far greater than erythrocyte phagocytosis in the several organs of the hemopoietic system. The engulfing of whole erythrocytes by the phagocytes of the hemopoietic system probably only occurs in acute cases of greatly increased blood destruction and then only for a short time. In the extreme type of blood destruction that follows the administration of hemolytic serum, for instance, Pearce and Austin (21) only found erythrocytes within the phagocytes for a few days in dogs, and Karsner, Amiral, and Bock (22) found in splenectomized cats that this phase was practically complete after 48 hours. Voegtlin, Hooper, and Johnson (23) have also observed it in acute T. N. T. poisoning of dogs, but here marked fragmentation of the circulating erythrocytes and in the perfusates of spleen, liver, and bone marrow was also found.

In the spleen and lymph nodes of our animals, minute granules of hemosiderin are here and there found in large numbers free in the pulp and sinuses, and even within the blood vessels. These observations tend indirectly to support Rous and Robertson's (24) view that erythrocytes are chiefly destroyed by fragmentation into hemoglobin-containing dust, which is then removed from the circulation by the phagocytes of several organs.

The sinuses of the spleen and lymph nodes are chiefly filled by myriads of endothelial phagocytes containing hemosiderin granules of varying size. They are also numerous in the splenic pulp and even scattered through the lymphoid tissue of the lymph nodes. In smaller amount hemosiderin-bearing phagocytes persist in animals that have not been transfused for many weeks whose blood picture

has returned to normal. Hemosiderin also is found extracellularly in large clumps, apparently from fusion of pigment from phagocytes.

In the liver, hemosiderin-containing cells are also prominent; from their position between the strands of liver cells many are apparently Kupffer cells, but others occurring in Glisson's capsule and in the portal vessels are obviously the usual endothelial phagocyte. Thrombosis of bile ducts and proliferation of bile capillaries and fibrous tissue are also found. The strands of liver cells are so compressed by the congested capillaries that in many places they remain atrophied after normal conditions have been restored. A similar condition is found in some lymph nodes, where the greatly distended sinuses practically fill the node so that there is very little lymphoid tissue remaining. Grossly, lymph nodes appear enlarged, reddened or reddish brown, with a purplish center. Histologically, many of these changes are seen to be due to great congestion of the blood vessels with accumulation of the above mentioned phagocytes. In other instances, however, erythrocytes are found, sometimes in great quantities both in the central and peripheral sinuses, mingled with the usual content of endothelial, lymphoid, and plasma cells. No evidences of hemorrhage are to be found, so that the appearance of a hemolymph node is strongly suggested. In the absence of special injections, this point cannot be definitely settled, but the impression remains strong that under the need for greatly increased blood destruction, structures resembling hemolymph nodes are developed.

The bone marrow exhibits not only the same pigment deposition, but also considerable cell hyperplasia. This was not found by Itami in plethoric animals and certainly the blood picture during life points to lessened erythropoiesis. In Boycott and Douglas' animals, on the other hand, Price-Jones found a definite cellular increase, though not necessarily of cells concerned in blood formation. If this increase were only of the leucocytic series it might be correlated with the leucocytosis constantly found; but erythroblasts and unidentified cells were also increased in number. The only observations we can offer in explanation are the lack of specificity of bone marrow response, to which attention has been called elsewhere, and the impossibility of determining in a cellular bone marrow just which cells are concerned with blood cell formation and which with blood destruction. Cer-

tainly the accumulation of hemosiderin, both intra- and extracellular, and the prominence of multinuclear giant cells in the bone marrows of recovered animals point to the importance of the bone marrow as an active agent in increased blood destruction. In the recovered bone marrow, not only were multinuclear giant cells unusually numerous, but so called mature elements (polymorphonuclears and normoblasts) were considerably more prominent than in animals killed during transfusion.

In the other organs examined no noteworthy lesions were found.

In the three splenectomized dogs (Nos. 1, 3, and 7) the same changes were found in the remaining hemopoietic organs, but they were more marked. In fact, the greater pigment content of these organs, coupled with the greater urobilin excretion, suggests from another point of view Asher's (25) unconfirmed contention that the anemia of splenectomy is due to a failure to reutilize the products of destroyed erythrocytes. The relatively greater bone marrow hyperplasia in these animals has been described elsewhere (26) as occurring after splenectomy. It should be noted again, however, that this is not necessarily either wholly or in part a sign of increased hemopoiesis. In the only dog actually killed by transfusions, the signs of blood destruction were no greater, but congestion of all organs was most extreme. In fact, in the lungs, spleen, and lymph nodes, large areas of packed erythrocytes gave a picture indistinguishable from hemorrhage. It was not possible, however, to establish conclusively the immediate cause of death in this animal.

In the rabbits of this series, the outstanding feature was the widespread evidence of agglutination and thrombosis. Not only is the sudden death apparently to be explained by the extensive intravascular agglutination of blood cells and pigment, but also evidences of former thrombi are to be found within the blood vessels and in the focal necroses and fibroses of liver and spleen. The frequency of these agglutination thrombi, as well as the general frailty of the rabbit, militates strongly against its usefulness in this kind of work if experiments are to be continued over a long period. The same deposition of blood pigment in the various organs was found as in the dog, with one exception. In the rabbit, as in human hemochromatosis, the blood pigment is found in two forms: the iron-reacting granules of

hemosiderin, and minute semiopaque spicules that fail to react to the usual iron tests (probably hemofuscin). This latter pigment is especially prominent in the protoplasm of the liver cells (which in dogs were never found to contain hemosiderin), but is also found in large amounts in the various sites already mentioned.

DISCUSSION.

The relationship of artificial plethora to bone marrow activity as indicated by the percentage of reticulocytes, emphasized in the case of rabbits by Robertson (3), has been confirmed in these experiments both with dogs and rabbits. We have found that with the development of plethora the reticulocytes in the blood decreased, and that after anemia developed a reticulosis was manifest in every case. During recovery from the experimental anemia the reticulocytes were present in greatest numbers. This would indicate that while "living blood" was being supplied in excess from outside, the normal factory for erythrocytes suspended operation; the slow resumption of activity when erythrocytes were needed during the period of anemia (about 1 to 2 weeks) points either to Itami's inactivity atrophy, or to a bone marrow-inhibiting influence that required considerable time for removal.

The urobilin excretion, which under the constant conditions of these experiments can be taken as a reliable index of blood destruction, began to rise in the feces soon after transfusions were begun. It was greater during the "plethoric anemia" than in extreme plethora, but quickly lessened after transfusion was stopped. Although urobilin could not be detected in the urine during the early stages of plethora, it appeared there simultaneously with the occurrence of extreme blood destruction. This accords with the findings of other investigators that fecal urobilin may be greatly increased before it appears in the urine.

Details of the manner in which blood is normally destroyed in the body are still open to question. It was hoped that the addition of large quantities of blood and the subsequent destruction of this excess blood would disclose the underlying mechanism of blood destruction. Phagocytosis has been considered as a possible means of blood destruction, and the importance of endothelial cells in the spleen and the

Kupffer cells of the liver has been pointed out by Pearce and Austin (21). Rous and Robertson (24) found an appreciable phagocytosis in dogs, but believe this would not suffice for normal blood destruction. It is unquestionable, however, that greatly increased phagocytosis of blood pigment occurs in artificial plethora, as it does in many forms of increased blood destruction. The fragmentation of erythrocytes, which they consider an important factor in the destruction of blood, was not observed by us in the circulation in amounts greater than that seen under normal conditions. It is, of course, possible that as we did not enter into the special procedures that they undertook, this may have played a greater part than we appreciate. The relation of the postmortem findings to this topic has already been discussed.

It is well known that parenteral introduction of certain foreign substances will cause the formation of antitoxins, agglutinins, and hemolysins, and that antibodies may sometimes be formed after injection of protein from the same species. It is quite obvious that the first of these factors, namely antitoxins, may be eliminated in these experiments. As previously mentioned, Robertson (3) and Kambe and Komiya (4) have shown the presence of antibodies capable of destroying erythrocytes, even of the same species, in large numbers during plethora in rabbits; and isohemolysins and isoagglutinins have been produced in cats after compatible transfusions (5).

In a further attempt to explain the mechanism of this "plethoric anemia" by the production of agglutinins or hemolysins, ten rabbits were transfused by us with 5 to 20 cc. of compatible rabbit blood daily, according to the method previously described. Their blood changes corresponded in the main with those we have reported in dogs, but at no time were we able to demonstrate the presence of isoagglutinins or isohemolysins. Thinking that in our previous study on dogs, antibodies might have developed, but been absorbed by the daily repeated injections, we discontinued transfusions on the anemic rabbits for varying lengths of time before the antibody tests were made. Carefully controlled quantitative tests, with the complement fixation method, still continued negative. We are therefore unable to aid in the solution of this phase of the problem, and have no explanation as to why, like Boycott and Douglas and other observers, we were unable to demon-

strate either agglutinins or hemolysins while blood was obviously being destroyed in greatly increased quantities and in spite of the fact that in the rabbits agglutinative thrombi were found at autopsy. Faulty technique, the most obvious explanation, we endeavored to guard against most carefully. The ability of transfused rabbits to survive was extremely slight for reasons already discussed under the section on pathological anatomy.

In regard to the effect of splenectomy on plethora, and on the consequent anemia, one cannot but be impressed by the more constant and striking anemia of the dogs splenectomized during the course of the transfusions (Nos. 6 and 7) than of those that were not splenectomized (Nos. 4 and 5). In view of Hektoen's demonstration (27, 28) that under certain conditions antibody formation is lowered after splenectomy, and of our inability to demonstrate antibodies at any time, this anemia of splenectomized dogs can hardly be based on such grounds; but we feel confident that some relationship exists between the loss of the spleen and the marked anemia that developed. It is also of interest that "plethoric anemia" is harder to produce in dogs than in rabbits, animals whose spleens are relatively much smaller (0.05 per cent of body weight as against 0.25 per cent of dogs).

The two chief points of interest in the blood volume studies are: (1) the confirmation of previous findings as to the constancy of the plasma volume under widely varying conditions, and (2) the remarkable adaptability of the organism in accommodating itself to rapid increases in total blood volume reaching as high as 250 per cent of the normal.

The metabolism studies have pointed out a marked retention of nitrogen by the organism for a long period of time. We are not able to learn from these experiments how and when this excess nitrogen is eliminated from the body. This retention and the failure of the hemoglobin to rise appreciably during the first 10 days of transfusions with a corresponding lack of increased nitrogen elimination would seem to indicate the existence of a mechanism for the storage of considerable excess blood and its decomposition products.

The possibility of finding a true plethora followed by anemia in clinical medicine is illustrated by a recent report by Freund (29) of a case studied in Krehl's clinic.

After incurring syphilis and other infectious diseases, the patient developed a typical Vaquez polycythemia of 135 per cent hemoglobin, and blood count of 9,200,000 red cells. Several months later the blood picture gradually changed to that of pernicious anemia, with megaloblasts, stippled red cells, normoblasts, and urobilinuria. This condition was next followed by exhaustion of the hemopoietic system with absence of nucleated red cells, myelocytes, and platelets, a steadily falling hemoglobin, and finally death from aplastic anemia.

SUMMARY AND CONCLUSIONS.

1. The effects of repeated transfusions of blood on the blood-destroying and blood-forming apparatus of normal and splenectomized dogs and rabbits have been described. An anemia which developed despite continued blood transfusions in two dogs splenectomized during plethora has also been studied.

2. The decrease or absence of reticulocytes from the blood stream during plethora and their increase during "plethoric anemia" are evidently due to depression and activation of bone marrow activity. The response of the bone marrow is not immediate upon the onset of anemia, but is delayed for several days.

3. The blood volume studies have served to emphasize the constancy of plasma volume under extreme experimental conditions, and the adaptability of the circulatory system to large increases in total blood volume.

4. Blood destruction and elimination, as measured by urobilin excretion, are greatly increased during the stage of plethora, but still more so during "plethoric anemia."

5. Despite intravenous introductions of large quantities of nitrogen in the form of whole blood, the total nitrogen, urea, and ammonia in the urine and feces are not raised appreciably for some time after the onset of plethora. The normal organism is apparently able to store large quantities of blood or its decomposition products. Upon the onset of a "plethoric anemia," there is an increase in urinary total nitrogen and urea excretion, which was lowered during the course of the anemia. Albuminuria is also found at this time. Other nitrogenous constituents and phosphates show no striking changes.

6. Blood pigment, chiefly in the form of hemosiderin, is deposited in enormous quantities in the spleen, liver, lymph nodes, and bone marrow. It occurs chiefly in phagocytes, though in late stages large

extracellular masses are found. Increased pigment deposition can still be found several months after transfusions have been stopped.

7. Phagocytes containing erythrocytes are found rarely, if at all, and only in the acute cases, but their occurrence may be greatly masked by the coexistent congestion.

8. In splenectomized dogs the tendency to "plethoric anemia" is much more apparent, although a direct connection between the two events is not established. In rabbits, whose spleens constitute only 0.05 per cent of body weight, "plethoric anemia" is more easily produced.

9. In splenectomized animals pigment-bearing phagocytes are especially prominent in the liver, although lymph nodes and bone marrow apparently share in the extra work caused by the absence of the spleen. Lymph nodes with some of the characteristics of hemolymph nodes were found in various localities in all animals that had been made plethoric.

10. In rabbits blood pigment is deposited in the hemopoietic organs in large amounts, but under the conditions of our experiments, the picture and the experiment have been constantly complicated by early fatal intravascular agglutination and thrombosis. In the rabbit, as in human hemochromatosis, the pigment is found in two forms: hemosiderin granules, and smaller, dark spicules that do not react to the usual iron stains (probably hemofuscin). The latter pigment is also found seeded through the cells of the liver parenchyma.

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PAROXYSMAL VENTRICULAR TACHYCARDIA

REPORT OF ONE CASE WITH NORMAL TYPE OF AURICULAR MECHAN-
ISM AND THREE WITH AURICULAR FIBRILLATION *

C. C. WOLFERTH, M.D. AND THOMAS M. McMILLAN, M.D.

PHILADELPHIA

Paroxysmal tachycardia of ventricular origin is one of the rarest disturbances of the cardiac mechanism. The first case with electro-cardiographic tracings was recorded by Lewis [1] in 1909. Robinson and Herrmann [2] recently reported four cases and discussed the criteria on which they consider a diagnosis justifiable. The points emphasized by these authors may be stated briefly as follows:

1. Electrocardiograms are necessary to differentiate ventricular tachycardias from those of auricular origin.

2. The condition is most clearly shown when a succession of auricular complexes can be made out occurring independently of and at a slower rate than the complexes of ventricular origin.

3. The ventricular complexes are distinctly abnormal in form; but this alone cannot be taken as absolute proof that the impulses are of ventricular origin, as changes in form may be caused by disturbances in intraventricular conduction.

4. The presence of isolated ectopic ventricular beats before or after a paroxysm is regarded as evidence in favor of the tachycardia being of ventricular origin, especially when the form of the complexes of the isolated beats is the same as the form of the paroxysm.

Lewis [3] has pointed out that in certain cases, tracings showing the beginnings of paroxysms are of great value in determining the origin of the abnormal beats. He states that several of the cases published are clear instances of paroxysms arising in the ventricles and are unmistakable because the first beat of the paroxysm has the same relations to the preceding normal rhythm as has a ventricular extrasystole.

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2. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart 8:59 (Feb.) 1921.

3. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1920.

Robinson and Herrmann, reviewing the cases previously reported, accept six as undoubted instances of ventricular tachycardia. These are the two cases of Lewis,[1, 4] and one each of Hart,[5] Butterfield and Hunt,[6] Vaughn[7] and Willius.[8] Cohn's case[9] is also an undoubted instance of the condition. Since Robinson and Herrmann's paper, three clear cases have been published by Gallavardin,[10] two by Singer and Winterberg,[11] one by Marvin and White[12] and one by Dieuaide and Davidson.[13] Singer and Winterberg designate the abnormal mechanism in one of their cases as extrasystolic arrhythmia bordering on paroxysmal tachycardia, but some of the periods of rapid rhythm, they state, persisted for at least 60 successive beats. The case should, therefore, be classed as one of paroxysmal tachycardia. The tracing of Dieuaide and Davidson's patient, taken five hours before death, shows an abrupt transition during complete heart block from a typical slow ventricular rate and complexes of supraventricular type to a rapid regular rhythm of ventricular origin. Bishop[14] has recently published tracings of a case (Case 1) in which the form of the ventricular complexes suggests that the beat is arising in a ventricle, but no other evidence in favor of that view is offered. A ventricular origin of the abnormal rhythm is also suggested by the form of the ventricular complexes in the tracings published by Barcroft, Bock and Roughton[15] in connection with the report of their studies of respiration and blood flow during paroxysmal tachycardia.

4. Lewis, T.: The Mechanism of the Heart Beat, London, 1911.

5. Hart, T. S.: Paroxysmal Tachycardia, Heart **4**:128 (Nov. 30) 1912.

6. Butterfield, H. G., and Hunt, G. H.: Observations on Paroxysmal Tachycardia, Quart. J. M. **7**:209 (April) 1914.

7. Vaughn, W. T.: A Study of Paroxysmal Tachycardia with Especial Reference to Tachycardia of Ventricular Origin, Arch. Int. Med. **21**:381 (March) 1918.

8. Willius, F. A.: Paroxysmal Tachycardia of Ventricular Origin, Boston M. & S. J. **178**:40 (Jan. 10) 1918.

9. Cohn, A. E.: The Present Status of the Electrocardiographic Method in Clinical Medicine, Am. J. M. Sc. **151**:529 (April) 1916.

10. Gallavardin, L.: Tachycardie Paroxystique Ventriculaire, Arch. d. mal. du coeur **13**:121 (March) 1920. Tachycardie Ventriculaire Terminale, Arch. d. mal. du coeur **13**:207, 210 (May) 1920.

11. Singer, R., and Winterberg, H.: Chinin als Herz- und Gefässmittel, Wien. Arch. f. inn. Med. **3**:329 (Nov. 15) 1921.

12. Marvin, H. M., and White, P. D.: Observations on Paroxysms of Tachycardia, Arch. Int. Med. **29**:403 (April) 1922.

13. Dieuaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrhythmias, Arch. Int. Med. **28**:633 (Nov.) 1921.

14. Bishop, L. F.: Early Signs of Fibrillation of Ventricle as Shown by Occurrence in Electrocardiogram of Periods of Ventricular Tachycardia, Ann. Med. **1**:58 (April) 1920.

15. Barcroft, J., Bock, A. V., and Roughton, F. J.; Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, Heart **9**:7 (Dec. 14) 1921.

In the cases thus far reported, four types of auricular mechanism in association with the tachycardia have been recognized. These are: (1) the normal type of auricular action in which the auricles are beating independently of and at a slower rate than the ventricles; (2) retrograde auricular beats due to the stimulation of the auricles from the ventricles; (3) auricular flutter and (4) auricular fibrillation. In some tracings, no waves due to auricular activity can be identified.

The combination of auricular flutter or fibrillation with paroxysmal ventricular tachycardia is extremely rare (except when the latter is caused by drugs), only one case of each having been reported, both by Gallavardin. Dieuaide and Davidson obtained a series of ectopic ventricular beats during the course of auricular fibrillation in a patient a few minutes before death. While the rate in their case was scarcely rapid enough to be classed as a tachycardia, it would appear that the mechanism was essentially the same as that found in paroxysmal ventricular tachycardia. This view is supported by the fact that brief series of ectopic ventricular beats of infrequent rate were also observed in Gallavardin's case of auricular fibrillation and paroxysmal ventricular tachycardia and in our Case 2 to be described later.

REPORT OF CASES

CASE 1.—M. H., negress, 20, a waitress, was admitted to the medical division of the University Hospital, Jan. 22, 1913, complaining of shortness of breath and palpitation of the heart. She stated that she had been "short-winded" as long as she could remember but otherwise had been as well as usual until five days before admission when suddenly, while working, she felt her heart beat, became weak, dizzy and short of breath and had a pain in her head. She also had a smothering sensation when she lay flat. These symptoms continued up to the time of her admission. She thought her abdomen had swollen since she had become ill.

Previous History.—She gave a history of having had measles, mumps, chickenpox, pneumonia, bronchitis and typhoid but no rhematism, chorea, tonsillitis or scarlet fever. There was nothing of importance in the social and family history.

Physical Examination.—The physical examination on admission showed slight cyanosis but no respiratory distress. Vigorous rapid pulsations in the neck were noted. The heart was definitely enlarged with a transverse measurement of 17 cm. No murmurs were heard. The cardiac rate was 190. Moist râles were heard at the bases of both lungs. The liver extended 4 cm. below the costal margin in the right midclavicular line and there was marked tenderness over it. There was slight pretibial edema.

Course.—The rapid heart action lasted until fourteen hours after admission when the rate dropped to 82. During the next few days there were numerous extrasystoles and at times a bigeminal pulse. Five days after admission there was another attack of tachycardia, which lasted sixteen and one-half hours, and two days later a third attack, lasting five hours. During the remainder of her stay in the hospital, a period of three weeks, there were no further attacks but extrasystoles were constantly noted. At the time of her discharge, she felt quite as well as she had before the onset of her illness.

Laboratory Examination.—Examinations of the blood and urine showed nothing of importance. The Wassermann reaction was negative.

Electrocardiograms were made by Dr. Thomas Cope both during the periods of tachycardia and in the intervals. A tracing made during a period of tachycardia (Fig. 1) shows ventricular complexes of a distinctly abnormal type. In Lead 2, waves due to the auricular activity can be made out and it is seen that the auricular contractions are occurring independently of and at a slower rate than the ventricular. In Figure 2, made during a period of slower heart action, is shown the supraventricular type of ventricular complexes. There are present a number of extrasystoles mostly auricular in origin. None of the ventricular complexes are similar to those found during the period of tachycardia.

CASE 2.—W. N., a white male, aged 61, was admitted to the Philadelphia General Hospital Feb. 1, 1922, showing the signs of some grave disturbance of the circulation. The breathing was Cheyne-Stokes in type.

Previous History.—The patient was dull, stuporous and quite irrational, and for this reason a precise history could not be obtained. However, it appeared that he had been breathless on rather moderate exertion for at least seven years, and at times had had edema. He had been able to continue his work as a motorman until Oct. 1, 1921, when he had to give up on account of breathlessness, cough and edema. No information could be obtained as to whether these symptoms had come on suddenly or not. The rest of the history elicited was unimportant except for a questionable attack of rheumatic fever at 25.

Physical Examination.—On examination, there was found to be extensive edema of the legs including the thighs, and also of the abdominal walls. There were signs of fluid in both pleural spaces, and questionable signs of ascites. The liver was greatly enlarged. The cardiac apex impulse was located in the fifth interspace 4 cm. outside the nipple line and 12.5 cm. from the midclavicular line. No murmurs were heard. On admission, the cardiac rhythm was found to consist of periods of rapid regular action with a rate of 164, followed by periods of irregular rhythm with a rate varying between 48 and 60. The two types of rhythm seemed to share the cardiac action about equally, each lasting usually from one to two minutes. The periods of tachycardia began and terminated abruptly. The pulse was barely perceptible and there was a large pulse deficit.

Laboratory Examination.—The urine showed signs of renal congestion, there being a cloud of albumin with a moderate number of casts. The specific gravity was 1.024. The blood urea nitrogen was 20 mg. per hundred cubic centimeters. The blood Wassermann was negative.

Treatment.—At the time of admission, a clinical diagnosis of auricular flutter was made, the periods of slow irregular heart action being attributed to varying degrees of A-V block. Accordingly the patient was given 4 c.c. of the tincture of digitalis followed six hours later by a similar dose. An electrocardiogram obtained eight hours after admission showed that the cardiac mechanism was slow auricular fibrillation interrupted by paroxysms of tachycardia with complexes of the ventricular type. The administration of digitalis was discontinued, and as far as could be determined, the medication did not influence the cardiac action in any way. The alternation of rapid regular and slow irregular action persisted as long as the patient lived.

The paroxysms of tachycardia were never of very long duration, the longest one timed being four minutes. As far as could be determined, there was no greater circulatory embarrassment during their presence than during the periods of slow rhythm. The patient was, however, conscious of the rapid beating of his heart. His condition gradually grew worse. Large amounts of fluid were removed from both sides of the chest but without improvement. The mental state became more confused, restraint being required to keep him in bed. February 8, following a violent vomiting spell, sudden death ensued.

The Electrocardiograms.—Many tracings were made from which have been selected those presented in Figures 3, 4, 5, 6 and 7, to illustrate the types of cardiac action observed. During the periods of slow irregular ventricular activity (Figs. 3 and 4) the auricles are observed to be fibrillating. There are

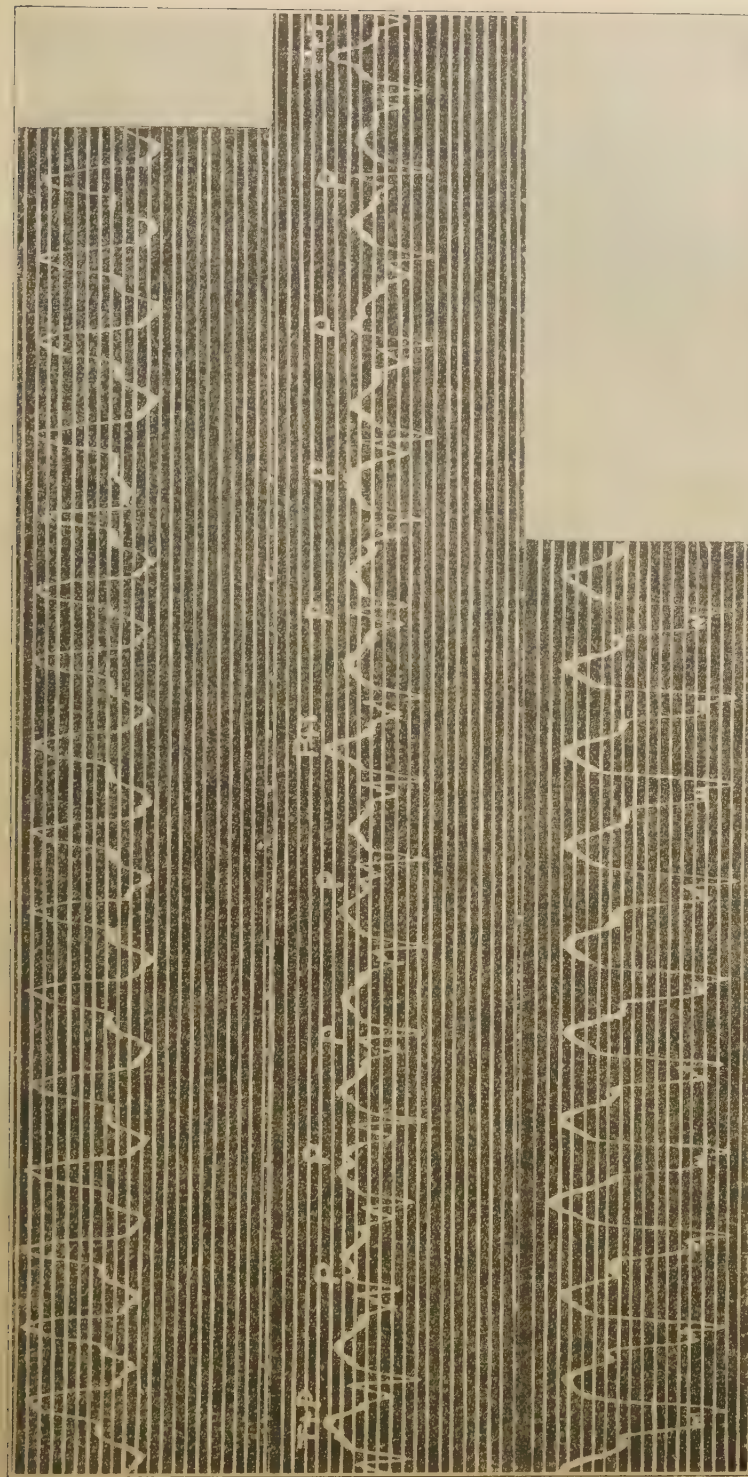Fig. 1.—Case 1. Tracing made during a period of tachycardia. The evidences of auricular action are distinct in Lead II, but are not discoverable in Leads I or III. The auricular rate is 125 and the ventricular rate 192. The photographic paper was not moving evenly. Retouched.
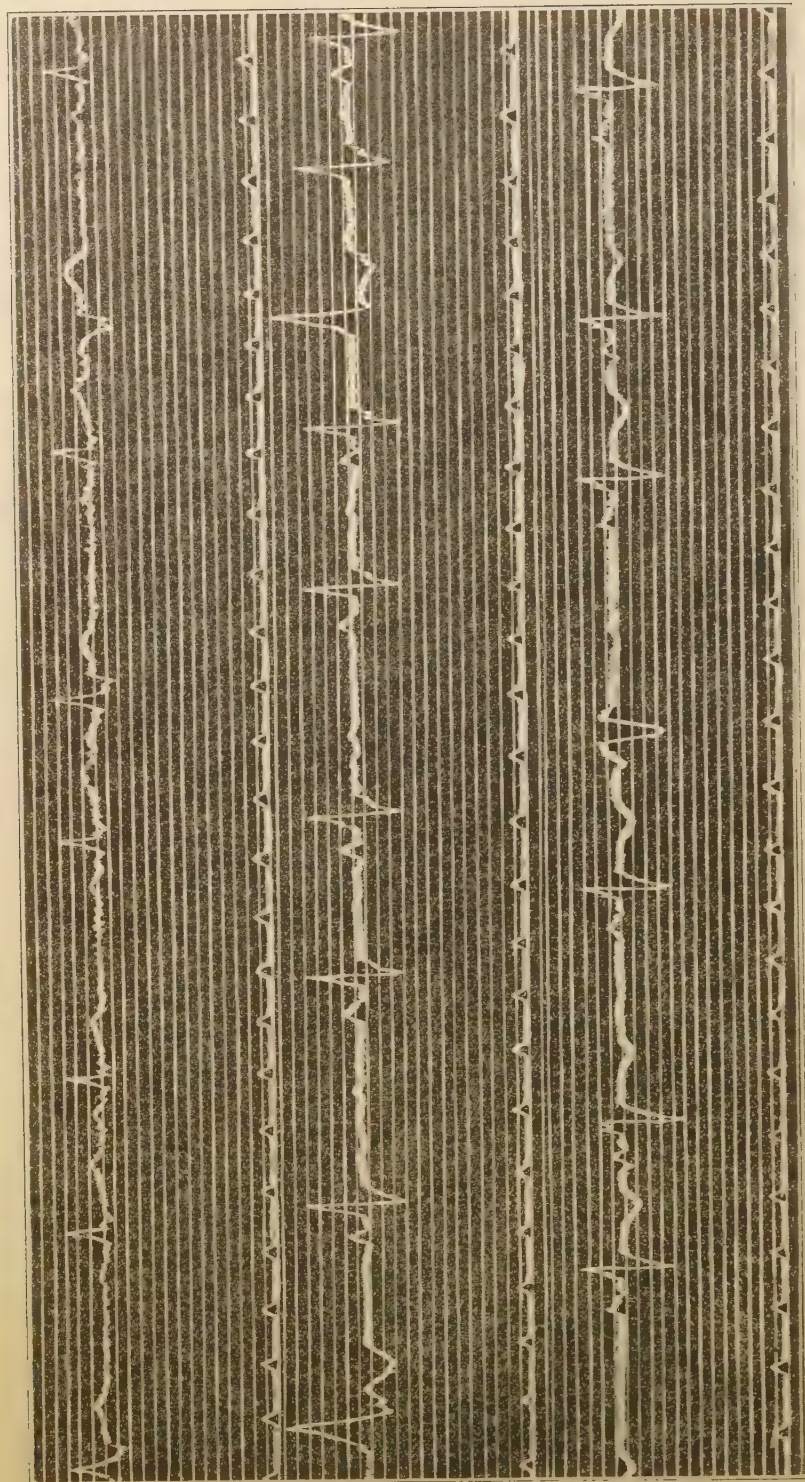
Fig. 2.—Case 1. Tracing made during an interval between attacks of tachycardia. Numerous extrasystoles, mostly of supraventricular type. Retouched.

numerous complexes of ventricular type; they are more frequent in some tracings than in others but at no time were more than six sequential complexes of supraventricular type recorded. In nearly every instance each beat of ventricular type is paired with the preceding beat in such a way that their relations are practically identical with those of the other couples in the same tracing. The time intervals between the first and second beats of the couples do not vary more than 0.01 or 0.02 second in any electrocardiogram, although slightly greater variations are observed in tracings made at different times. Occasionally all the beats were coupled (Fig. 5) and gave an element of regularity to the arrhythmia.

During the periods of tachycardia (Figs. 4 and 6) all the complexes are of ventricular type and similar in form to the second of the paired beats. Figure 4 shows the onset of paroxysms. In each instance, the relations of the first complex of ventricular type initiating the paroxysm to the preceding supraventricular complex are the same as those of paired beats, and the time intervals are the same.

All tracings of the first few beats of paroxysms show slight irregularity of ventricular action. This is more marked in some paroxysms than others and in Figure 6 an extreme instance of this irregularity is seen. In the short paroxysms, the ventricular action was slightly arythmic throughout but in the longer ones, it invariably settled down to a perfectly regular rhythm. At the offset, there tended to be slight slowing (Fig 4) which was particularly marked in the last cycle before the resumption of the slow action.

Case 3.—E. J., white, male, aged 18, was admitted to the Medical Division of the University Hospital Sept. 10, 1921, complaining of weakness and swelling of the abdomen and legs. He stated that at the age of 5 he had had an attack of acute articular rheumatism which kept him in bed for several months. He recovered entirely but three years later had an illness in which there was high fever and his heart was affected. After this he was always weak and had palpitation on exertion. From the age of 13, there were periods of cardiac breakdown every year which kept him away from school for a part of the time. The attack which brought him to the hospital was worse than any of the previous ones and instead of improving after rest in bed as he had done before, he gradually lost ground during a period of three months. He was very weak and short of breath and troubled by palpitation. There had been increasing swelling of the legs and abdomen and shortly before admission, of the left arm.

Physical Examination.—The patient was a fairly well developed boy for his age. He was orthopneic and somewhat cyanotic. There was marked edema of the legs and flanks. The left arm was greatly swollen, but the right appeared normal. There was a small aneurysm of the outer end of the innominate artery.[16] The liver was markedly enlarged and there was moderate ascites. The heart was tremendously enlarged, the area of percussion dulness extending from 6 cm. to the right of the midsternal line to the left midaxilla. There was a short systolic murmur at the apex. The ventricular action appeared to be totally irregular except for occasional runs of regular rhythm lasting a few seconds to nearly a minute. The rate during these periods of regular rhythm was counted a number of times and was always found around 140. During the periods of irregular rhythm, the rate was much slower.

Laboratory Examination.—The urine showed a cloud of albumin and numerous hyaline, light and dark granular casts. The phenolsulphonephthalein excretion in two hours was 25 per cent., and the blood urea nitrogen 60 mg. per hundred cubic centimeters. The blood count was normal, except for a slight leukocytosis of 12,900. The blood Wassermann was negative.

Course.—The patient remained in the hospital for ten days, but after the second day, no more of the short runs of regular tachycardia were noted and the ventricular action appeared to be continuously irregular. Digitalis was used freely but apparently without effect. He died ten days after leaving the hospital.

16. To be reported elsewhere.

Fig. 3.—Case 2. Auricular fibrillation, slow ventricular rate and one complex of ventricular type. The usual type of cardiac action observed between paroxysms of tachycardia.
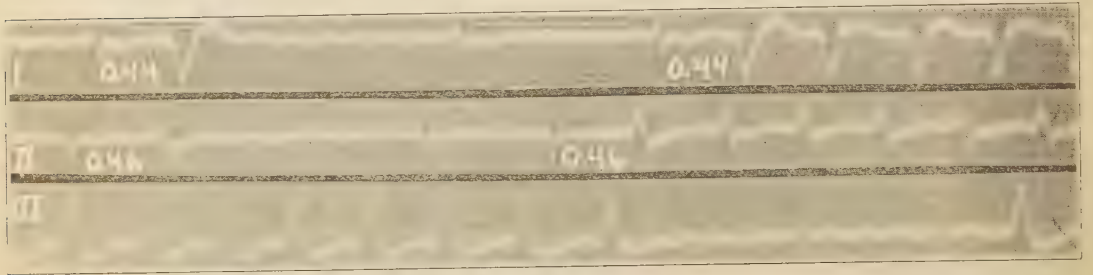
Fig. 4.—Case 2. Leads I and II show the onsets of paroxysms and Lead III an offset. The paroxysms are initiated by two beats identical in their relationships with the isolated coupled beats. The rhythm at the beginning of paroxysms is not quite regular. There is lengthening of the last cycle before the offset.
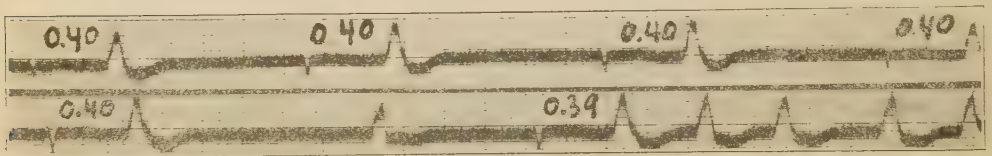
Fig. 5.—Case 2. Continuous tracing, Lead III. Five pairs of coupled beats in succession, an isolated complex of ventricular type and a short paroxysm initiated by a pair of coupled beats. The short paroxysm is quite irregular.
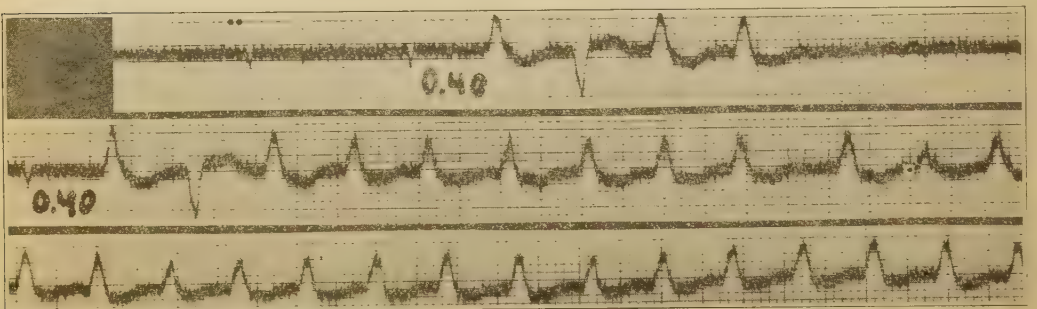
Fig. 6.—Case 2. Continuous tracing, Lead III. Unusual duration of irregularity at the beginning of one of the longer paroxysms.

Clinical Diagnosis.—Chronic rheumatic myocardial disease, cardiac failure, passive congestion; thrombosis of the left axillary vein; aneurysm of the innominate artery, probably mycotic in origin; chronic diffuse nephritis. The clinical diagnosis of the arrhythmia was auricular flutter, the periods of regular rhythm being interpreted as two to one *A-V* block. This view was favored by the fact that, on the day of admission, having the patient sit erect was often followed by short periods of regular tachycardia with a rate always around 140.

Electrocardiograms. — These showed that the clinical diagnosis of the arrhythmia was incorrect. All the tracings made except one showed auricular fibrillation and occasional complexes of ventricular type. The one unusual tracing (Fig. 8) shows the end of a period of rapid regular rhythm with complexes of ventricular type. At the offset of the paroxysm, auricular fibrillation is again evident. The tracing also shows three pairs of coupled beats shortly after the termination of the paroxysm. The time intervals between the first and second of the paired beats were 0.43, 0.42 and 0.43 second, respectively. The form of the complexes of isolated beats of ventricular type, the paroxysm of tachycardia and the second of the paired beats following the paroxysm are all the same. The cardiac rate during the paroxysm was 136, the length of the ventricular cycles being 0.44 second.
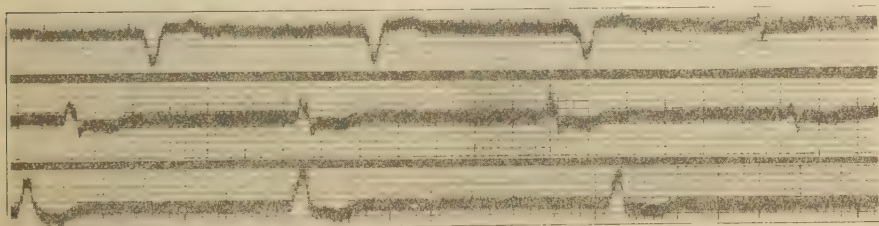
Fig. 7.—Case 2. Leads I, II and III. Brief periods of successive beats of ventricular type recurring slowly and somewhat irregularly.

CASE 4.—E. W., a woman, aged 58, was admitted to the medical Division of the University Hospital July 3, 1921, complaining of goïter and swollen legs. She stated that she had first noticed enlargement of the neck about seven years previously and for five or six years had had some difficulty in swallowing. For a few months before admission she had been nervous, suffered from cardiac palpitation, precordial pain and a feeling of oppression and shortness of breath on slight exertion. She had lost 17 pounds in the last ten months before admission.

Physical Examination.—She was a moderately emaciated woman appearing to be about the age stated. The thyroid gland was enlarged, particularly the right lobe. In the region of the isthmus, there was a mass the size of a walnut and directly above a small mass apparently attached to the larynx. The heart was greatly enlarged and had a transverse measurement of 16 cm. There was a systolic murmur at the apex. The rate was very rapid and the rhythm apparently totally irregular. A few crackling râles were heard at the bases of both lungs, the liver was enlarged and there was moderate swelling of the legs.

Laboratory Examination.—The blood and urine examinations showed nothing of importance. The metabolic rate was 37.7 per cent. above the normal. The blood Wassermann was strongly positive.

Clinical Diagnosis.—Syphilis, adenoma of thyroid, chronic myocardial disease, cardiac failure with passive congestion and auricular fibrillation.

An electrocardiogram (Fig. 9) confirmed the diagnosis of auricular fibrillation, but showed in addition a paroxysm of six rapidly recurring beats in which the complexes were of ventricular type. An isolated complex of the same type occurred shortly after the paroxysm and the time interval between it and the preceding beat (0.38 second) is equal to that between the first beat of the paroxysm and the beat preceding it. The rhythm, during the paroxysm, was not quite regular.

Treatment.—The patient received quinidin sulphate and the normal rhythm was restored within two days. While a tracing was being made shortly after the resumption of normal rhythm, a short paroxysm of rapid rate with wide excursions of the string shadow of the galvanometer was observed but could not be recorded. No more paroxysms were observed.

Improvement was rapid following the restoration of normal rhythm, and cardiac compensation was quickly restored. Antisyphilitic treatment was then given. The patient left the hospital after a stay of three weeks, and six months later reported to a social worker that she was well. She refused, however, to return to the hospital for further study.

DISCUSSION

In Case 1, the requirements of Robinson and Herrmann for the diagnosis of paroxysmal ventricular tachycardia are satisfied. The ventricular complexes are distinctly abnormal during the paroxysms, their form being that of contractions arising in the left ventricle. The auricular beats are independent of the ventricular and occur at a slower rate. This is the fifth case to be reported in which the waves of independent auricular contractions have been recognized during the paroxysms. The other cases are those of Butterfield and Hunt, Cohn, Robinson and Herrmann, and Gallavardin. In the two cases reported by Lewis in which the paroxysms were very brief, the auricular rhythm did not appear to be disturbed although no auricular waves were discernable during the paroxysms.

The Recognition of Beats of Ventricular Origin During Auricular Fibrillation.—In the presence of auricular fibrillation, the diagnosis of abnormal ventricular mechanisms such as ventricular extrasystoles or ventricular paroxysmal tachycardia lacks the confirmation that may ordinarily be obtained from an analysis of the auricular action. The origin of a single beat with an abnormal complex during fibrillation may be quite uncertain since temporary intraventricular defect in conduction may cause a beat of supraventricular origin to simulate a ventricular extrasystole. Under certain conditions however, as Lewis [3] has pointed out, the diagnosis of ventricular extrasystoles during fibrillation can be made beyond a reasonable doubt. Such is the case when (1) there is coupling of beats, (2) the first beat of the couple has a complex of supraventricular type and the second of ventricular type and (3) the various paired beats correspond to one another in their relations, including the time interval between the two beats. These conditions are abundantly fulfilled in our Case 2 and the second of the numerous paired beats observed may be regarded beyond reasonable
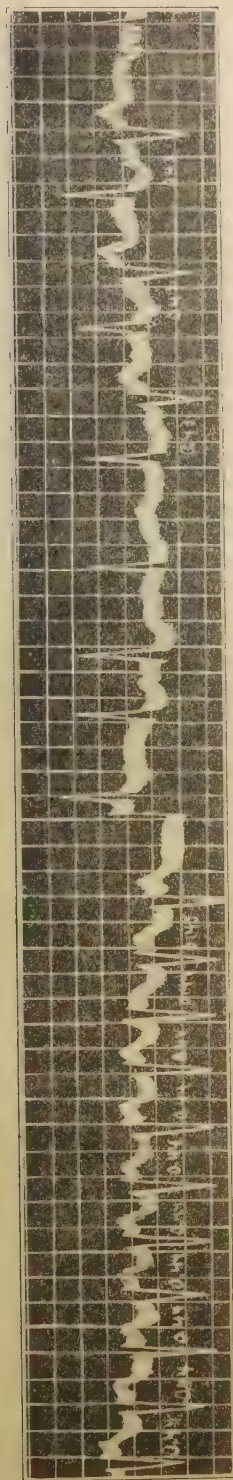
Fig. 8.—Case 3. End of a paroxysm of tachycardia (Lead I). At the right, three pairs of coupled beats, the second beat of each couple having complex identical in form with those found during the paroxysm. The ventricular rate during the paroxysm is 136. Retouched.
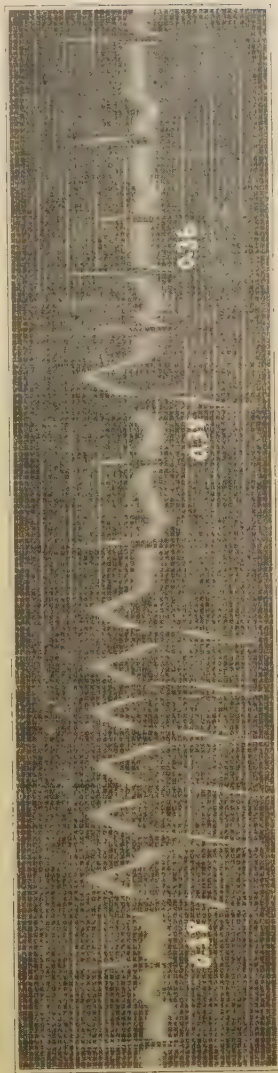
Fig. 9.—Case 4. Lead III. Short paroxysm of beats with complexes of ventricular type. The isolated beat of ventricular type is coupled with its preceding beat as is the first beat of the paroxysm. A complex of supraventricular type is more premature than the abnormal complexes.

doubt as being ventricular. If the tracings showing the beginnings of paroxysms be compared with the coupled beats, it will be observed that each paroxysm is initiated by two beats that are in all respects similar to the isolated couples. Following the second beat, there is found a succession of ventricular complexes having the same form and consequently portraying the same course of the excitation wave. Thus the origin of the paroxysms may also be regarded justifiably as ventricular.

In Case 3, the evidence is similar to that of Case 2, although not quite so complete since no tracing of the beginning of a paroxysm was obtained. There was the same type of coupling of beats and the complexes during the regular tachycardia were identical in form with the second complex of the couples. Furthermore, the ventricular cycles were approximately equal to the time intervals between the first and second beats of the isolated couples. In Case 4 there was similar coupling and the beats initiating the paroxysm were identical in their relations with those of the isolated couple seen in the same tracing (Fig. 9). Moreover, there are found complexes of supraventricular type more premature than the ventricular complexes, a fact that can- - not be explained on the assumption that the abnormal complexes represent merely aberrant beats due to intraventricular conduction changes.

The Auricular Mechanism During Paroxysms in Cases 2, 3 and 4.— Although no evidence of auricular activity could be discovered in tracings of paroxysms in Cases 2, 3 and 4, there is no reason to doubt that fibrillation continued. Fibrillation was undisturbed by coupled beats in all three cases and by short paroxysms in Cases 2 and 4. In relation to longer paroxysms in Case 2, the auricles were demonstrated to be fibrillating up to the onset of the ventricular tachycardia and immediately after the offset. Fibrillation was also present immediately after the offset in Case 3. Moreover, in Cases 2 and 3, no other auricular mechanism was discovered. A similarly close relationship of fibrillation to paroxysmal tachycardia was also observed in Gallavardin's case.

The Rhythm of Ventricular Paroxysms.—The fact that slight but definite ventricular irregularity was present throughout the paroxysm in Case 4 does not constitute a valid objection to the interpretation of its ventricular origin. As stated above, a similar irregularity was noted in the short paroxysms in Case 2 and also during the first few beats of the longer paroxysms. The brief paroxysms in Hart's and Cohn's cases also show ventricular irregularity as do the first few beats of a paroxysm recorded by Marvin and White. Thus a high percentage of the cases in which onsets of paroxysms have been recorded, show some ventricular irregularity.

The Length of Paroxysms.—The length of paroxysms of ventricular tachycardia appears to vary as widely as in the supraventricular types. A succession of two ventricular extrasystoles is often found and three occur occasionally. It has not been customary however, to regard less than six successive beats as a paroxysm and these are rare. In about half the cases thus far reported, none of the paroxysms observed exceeded five minutes in duration. Some cases had both short and long paroxysms, and occasionally the tachycardia has lasted for days. The longest case on record is the one reported by Robinson and Herrmann in which an attack lasted presumably for eleven days.

Association with Myocardial Disease.—It is evident from a study of the cases that paroxysmal ventricular tachycardia is usually associated with grave cardiac disease. Of twenty-two undoubted cases, eleven patients are known to have died within a short time after the ventricular tachycardia was recognized. There is abundant experimental evidence that the condition may be produced by coronary occlusion and Robinson and Herrmann have presented clinical evidence to that effect. Cardiac syphilis has been found in some cases. Occasionally, however, the condition has occurred in patients with a fair degree of cardiac function and without clinical evidences of profound myocardial disease. Most of such cases have been among those with short paroxysms.

Other Abnormalities of Cardiac Function.—The frequent occurrence of other disturbances of the cardiac mechanism has been a remarkable feature of the cases. Between paroxysms, extrasystoles are usually numerous. Most often these are ventricular in type and have electrocardiographic complexes similar in shape to those of the paroxysms. However all types of extrasystoles may be found. Various grades of *A-V* block up to complete block have been observed and also disturbances in bundle branch conduction. Three of the cases also had paroxysms of supraventricular types of tachycardia, four had auricular fibrillation (including the three of this report) and one, auricular flutter.

Clinical Manifestations.—Occasionally during brief paroxysms, as in our Case 4, the patient is unaware of anything unusual occurring, but in the majority of cases there are obstrusive symptoms. Palpitation, particularly a consciousness that the heart is beating very rapidly, is most common. In the longer paroxysms, the symptoms of cardiac failure become prominent features. The studies of Barcroft, Bock and Roughton on blood flow and respiration were made in a patient in whom, whatever the origin of the tachycardia, the excitation wave was spreading in an abnormal manner similar to that observed in ventricular paroxysms. These studies show what an extraordinary diminu-

tion of circulatory efficiency may occur during such a paroxysm. It is easy therefore, to understand the seriousness of a long paroxysm of ventricular tachycardia in a patient already the victim of myocardial disease.

As indicated previously, there is no way at present of distinguishing ventricular paroxysms from those of supraventricular type, except by electrocardiograms. From the history and the examination of the heart during a period of rapid rhythm, it should be possible in practically all cases to recognize the presence of some form of paroxysmal tachycardia. One can however scarcely eliminate the possibility (remote as it may be) of paroxysmal auricular flutter. When the paroxysms occur in association with auricular fibrillation, the ventricular action may closely simulate that of an ordinary form of auricular flutter, the paroxysms being mistaken for two to one rhythm and the slower irregular action for the inconstant block that so often occurs in flutter. This happened in our Case 3 and the clinical diagnosis of flutter appeared to be further confirmed by having the patient sit erect, which sometimes brought on the periods of rapid regular ventricular action thought to be two to one flutter, but was in reality paroxysms of ventricular tachycardia. Although the diagnosis of auricular flutter was also made in Case 2, it is apparent, on reflection, that the occurrence of paroxysmal tachycardia originating below the auricles, should have been suspected. The marked discrepancy in rate between the periods of rapid regular rhythm and the slow irregular action were greater than are to be expected to occur spontaneously as a result of change of A-V conduction in auricular flutter. Moreover, the conspicuous coupling of beats during the periods of slow action should have directed attention to the possibility of the rapid rhythm being of the nature of paroxysmal tachycardia.

The Influence of Drugs.—Recently, several papers have appeared suggesting that drugs such as quinidin and digitalis may be responsible, in certain cases, for ventricular tachycardia. Oppenheimer and Mann [17] state that a patient under their observation twice developed ventricular tachycardia during the administration of quinidin. Lewis, Drury, Wedd and Iliescu [18] report that abnormal ventricular complexes are frequent in electrocardiograms during quinidin treatment and that, in occasional cases, they become very numerous and are then associated with long or short periods of ventricular tachycardia. These authors have published a tracing in which a period of tachycardia was recorded

17. Oppenheimer, B. S., and Mann, H.: Results with Quinidin in Heart Disease, abstr., J. A. M. A. **78**:1758 (June 3) 1922.

18. Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations upon the Actions of Certain Drugs upon Fibrillation of the Auricles, Heart **9**: 207 (April 30) 1922.

and they have stated that they were inclined to view the abnormal complexes not as aberrant forms but more comparable to the abnormal beats which help to constitute digitalis coupling. Levy [19] reports that he has recorded ventricular tachycardia in five out of twenty-five cases of auricular fibrillation treated with quinidin.

Schwensen [20] recently reported two cases that he believed to show ventricular tachycardia as a result of the administration of digitalis. Unfortunately, in one of his cases, no tracing was obtained during the period of tachycardia. In the other case, auricular fibrillation was interrupted by a regular tachycardia, the tracing of which showed a remarkable alternation of complexes. The author's assumption of their ventricular origin cannot, however, be accepted as established.

Of the four cases we report, tachycardia due to digitalis or quinidin can be ruled out in Cases 1, 2 and 4, since neither of these drugs had been taken when the tachycardia developed. This is noteworthy particularly in Cases 2 and 4 in both of which accurate coupling of beats occurred. It should, however, be emphasized that this is not necessarily a digitalis effect. We have observed it also in other cases not under the influence of the drug. In Case 3, the possibility that digitalis caused the tachycardia could not be excluded, since treatment has been received before admission to the hospital. This, however, seemed unlikely, as large doses of the drug were administered in the hospital, in spite of which no paroxysms were observed after the second day.

In view of the observations of Oppenheimer and Mann, Lewis, and Levy on the ability of quinidin to evoke ventricular tachycardia, it is of interest to note that quinidin and quinin have been found of value in suppressing the condition. Boden and Neukirch [21] state that they were successful in terminating paroxysms by the intravenous injection of quinidin, while Singer and Winterberg [11] obtained good results in their cases with quinin. In our Case 4, both the auricular fibrillation and ventricular tachycardia were abolished by quinidin. These results would appear to indicate that further observations of the effects of the cinchona alkaloids in this condition are desirable.

SUMMARY

1. Four cases of paroxysmal ventricular tachycardia are reported, one with auricular mechanism of normal type and three with auricular fibrillation.

19. Levy, R. L.: The Clinical Toxicology of Quinidin, abstr., J. A. M. A. **78**:1919 (June 17) 1922.
20. Schwensen, C.: Ventricular Tachycardia as the Result of the Administration of Digitalis, Heart **9**:199 (April 30) 1922.
21. Boden, E., and Neukirch, P.: Klinische und experimentelle Beobachtungen über die Herzwirkung des Chinidins, Deutsch. Arch. f. klin. Med **136**:181 (June) 1921.

2. The electrocardiographic findings through which the diagnosis was arrived at in these cases are discussed. Emphasis is placed on the value for diagnosis, when the auricles are fibrillating, of comparing the relations of coupled beats to the onsets of paroxysms.

3. The literature is reviewed and from the study of the cases previously reported together with those here presented, the following data have been assembled: (*a*) Twenty-two cases have thus far been reported in which electrocardiograms justify the diagnosis of paroxysmal ventricular tachycardia. (*b*) During paroxysms, the following types of auricular action have been recognized: (1) normal mechanism; (2) retrograde auricular beats; (3) auricular flutter, and (4) auricular fibrillation. (*c*) Slight irregularity of rhythm just after the onset of paroxysms is not unusual. It may also occur just before the offset. (*d*) In about half the cases reported, none of the paroxysms observed exceeded five minutes in length. The longest paroxysm reported apparently lasted for eleven days. In long paroxysms, severe cardiac failure usually occurs. (*e*) Profound myocardial disease is usually associated. Other disturbances of the cardiac mechanism are remarkably frequent. Eleven of the twenty-two patients are known to have died shortly after coming under observation. (*f*) Short paroxysms occurring during auricular fibrillation may cause the ventricles to behave in a manner simulating auricular flutter and lead to a mistaken diagnosis of flutter. (*g*) The results of quinin and quinidin in treatment have been promising, but further observations are necessary in order to determine whether or not these drugs are of real value in this condition.

NOTE.—Since this paper has gone to press, another case has been reported by Gallavardin (Extra-systolic ventriculaire a paroxysmes tachycardiques prolonges, *Arch. d. mal. du cœur* **15**:298 [May] 1922), in which were recorded brief successions of extrasystoles and long attacks of tachycardia, both apparently arising from the same focus. During the long paroxysms, the auricular action was sometimes independent, and at other times controlled by retrograde conduction from the ventricles.

PRESENTATIONS AT

PATHOLOGICAL SOCIETY OF PHILADELPHIA.

INFARCTION IN AN AMYLOID SPLEEN ILLUSTRATING THE RESISTANCE OF AMYLOID MATERIAL TO AUTOLYSIS.

BALDUIN LUCKÉ, M.D.

Certain protein substances, particularly amyloid, resist to a marked degree putrefactive and autolytic influences and the solving action of weak acid. Pure amyloid may readily be obtained from tissues infiltrated with this substance by artificially digesting the tissues with weak acids. In postmortem degenerated organs any amyloid present is usually well preserved and gives specific staining reaction, while even the fibrous tissues are more or less destroyed and no longer allow selective staining. The organ exhibited is a sago spleen from a woman who suffered with repeated attacks of valvular endocarditis. Several anemic infarcts are present in the spleen; some have undergone softening; others are firm. In the infarcted areas the amyloid follicles stand out quite as conspicuously as in the noninfarcted regions, and take on a deep brown color upon application to the surface of Lugol's solution. Sections were stained with hematoxylin and eosin, Mallory's anilin blue and with methyl violet. It was found that while the amyloid substance in the necrotic areas still reacted to the stains mentioned, they took a somewhat paler tint.

BLOOD SAMPLING FOR CHEMICAL ANALYSIS.

W. H. STONER, M.D.

(From the Biochemical Laboratory Philadelphia Hospital.)

Previous diet and exercise are standardized. The pneumatic tourniquet of the sphygmomanometer is employed to constrict the venous but not the arterial circulation. The Meeker needle, which

has an equal lumen section throughout and is sharp only at the extreme point of an obtuse bevel, is used to withdraw any desired quantity of blood into a test-tube coated with sodium oxalate, 0.5 mg. for each cc of blood.

THREE CASES OF AORTIC ANEURYSM.

E. A. Case, M.D.

A. *Fusiform Aneurysm.* D. T., laborer, negro, aged forty-two years. Philadelphia General Hospital, service of Dr. Brinton. Autopsy, January 19, 1920.

The aneurysm began at the aortic valve and involved the arch with its ascending and descending limbs.

The wall of the aorta was intact, the intima the seat of advanced sclerosis with atheroma and the aneurysm large enough to admit one's fist. The thyroid cartilage and trachea were deviated to the right, and during respiration the excursions of the former were marked. No record of a Wassermann reaction.

B. *Saccular Aneurysm.* W. H., laborer, negro, aged forty-two years. Philadelphia General Hospital, service of Dr. Stevens. Autopsy, February 2, 1920.

Four weeks before admission to the hospital the patient noticed a swelling, about the size of an egg, beside the spinal column. For two weeks this swelling increased rapidly in size and then remained stationary. Pain was experienced for a short time each evening. The Wassermann reaction was four plus.

At the beginning of the descending limb of the aortic arch there is a saccular dilatation about 20 cm. in diameter. An opening in the posterior wall of this sac communicates with a large mass of clotted blood which had gradually accumulated beneath the pleura, dissecting it from the ribs, pushing the lung forward and extending into and below the left axillary region. Posterior to and below the left axilla the skin was discolored and thin, suggesting imminent rupture.

C. *Dissecting Aneurysm.* J. M., white, aged seventy-six years. Philadelphia General Hospital, service of Dr. Ingham. Autopsy, January 5, 1920.

The intima of the aorta is sclerotic and atheromatous. Twelve cm. above the celiac axis there is a shallow, circumscribed dilatation 2 cm. in diameter, the lower border of which is thrown up into a ridge forming a kind of shelf. This saccular aneurysm contains a thrombus.

Eight cm. above the celiac axis there is a rounded opening 2 cm. in diameter, with smooth, rounded edges leading into a cavity 7

cm. long by 3.5 cm. in diameter, filled with a thrombus. One and one-half cm. below this opening there is another and smaller one, also communicating with the same aneurysmal sac, so that a probe introduced through one opening would enter the sac and emerge at the other one.

The outer coat of the aorta is apparently intact, and it is probable that the blood entering the upper opening dissected a passage in the wall of the aorta and emerged at the lower orifice, forming at the same time a circumscribed aneurysm.

SPECIMEN OF LEIOMYOMA OF THE INTESTINE IN A CASE OF FIBROMA MOLLUSCUM.

Morton McCutcheon, M.D.

This specimen is from a white woman, who died, at the age of eighty-five years, following cellulitis of the hand.

At autopsy, the skin presented the typical appearance of fibroma molluscum with hundreds of fibrous tumors on all parts of the body. They were somewhat less frequent on flexor than on extensor surfaces. On the forehead, the nodules were so close together as to give a leonine expression. Aside from livor mortis, there was no discoloration of the skin.

The clinical notes stated that no pain or other subjective disturbance had been caused by the tumors.

The uterus contained small intramural and submucous fibroids.

On serous surface of the stomach were numerous small fibrous nodules, the largest 5 mm. in diameter In small intestine were a number of submucous tumors.

The gross specimen exhibited is a strip of ileum, on the mucous surface of which is a small, firm, pedunculated, gray tumor, 8 by 5 by 3 mm.

Histologically, the skin tumors are soft fibromas. Section of intestine shows a new growth 5 by 2 mm. between the transverse and longitudinal layers of muscle. The latter layer is interrupted by the tumor, surviving muscle strands being scattered through the new growth.

The tumor itself consists of three elements: (1) Predominating are interlacing bundles of fine fibrils, which stain with eosin, and with van Gieson's stain take the picric acid faintly; the fibrils are provided with numerous spindle-shaped nuclei; some of these have rounded ends, some pointed. (2) A very fine network of fibrous connective tissue, which is colored red by van Gieson's method; this fibrous tissue is considerably less in amount than the yellow staining fibers. (3) Numerous capillaries lined with endothelium.

Predominating fibers staining with picric acid are evidently smooth muscle, so that the diagnosis of the specimen is leiomyoma.

Conclusions. Several cases of fibroma molluscum have been reported, with fibrous tumors along gastro-intestinal tract. At least in the present case, these intestinal tumors are found not to be fibromata but leiomyomata.

HEMATOMA OF BOTH RECTUS ABDOMINALIS MUSCLES.

Balduin Lucké, M.D.

In a number of infections, such as typhoid, smallpox, streptococcic infections, tetanus, etc., as well as after severe burns or in persons frozen to death, a peculiar degeneration of various voluntary muscles is encountered which is sometimes accompanied by rupture of the affected muscles and the formation of hematomata. Such lesions were met with particular frequency during the epidemic of influenza of 1918–1919. The writer in about 400 autopsies on soldiers, between the ages of eighteen and thirty-one years, who died of various acute infections, found muscular degeneration of marked degree, associated with hematoma, in about 6 instances. Lighter grades of degenerations are more frequently encountered and often overlooked.

The muscles most often involved are the abdominal recti, the adductors of the thigh and the pectoral muscles. Usually the lesions are patchy or streaky, picking out groups of fibers, which because of the resulting alteration stand out quite distinctly from the surrounding normal muscle. The affected areas may attain the size of several centimeters. Various degrees of degeneration may usually be seen in the diseased portions. The earliest recognizable change consists of mere dulling and loss of translucency. Later the diseased fibers became distinctly gray-brown or of a dirty clay color; their elasticity is lost and they become softened.

Such areas, being points of lessened resistance, are frequently invaded by bacteria which produce further destruction resulting in abscess formation. Thus one may often explain the muscle abscesses found in influenza and other bacterial diseases.

Rupture of the softened fibers may occur, the lower portion of the recti being the usual point where this takes place. Blood will then escape into the gap and a hematoma, sometimes of large size, result.

Microscopically, one finds usually no inflammatory reaction in the earlier stages. The process seems, therefore, to be of toxic nature. Later a leukocytic infiltration and a fibrin exudate is generally encountered. The involved fibers are at first swollen,

take a deep eosin stain, lose their striations and nuclei, and have a glassy, hyaline appearance. Later the staining properties are altogether lost, and the degenerated substance is often vacuolated. The sarcolemma usually exhibits proliferative alterations, and more or less complete reorganization seems to take place. If the degenerated area is very large, as in actual rupture, a considerable inflammatory reaction occurs. Here a fibrin network, often containing many leukocytes and bacteria, is encountered. Sarcolemnal and fibroblastic proliferation takes place, no restitutio ad integram results, but the gap may be bridged by scar tissue.

These lesions are often spoken of as Zenker's coagulation necrosis or as muscle-hyaline degeneration. They explain certain abdominal pains in patients with typhoid and other infectious fever. The writer feels that these lesions also possess great medico-legal interest for the ruptured muscles appear usually as if torn by violence, and the question of possible trauma may arise. The absence of cutaneous discoloration may often exclude injury, but it does this only in a relative sense.

The muscles exhibited came from a white male, aged forty-three years, who died from postinfluenzal streptococcic lobular pneumonia. Both recti are torn 5 cm. above the pubic bones. A large hematoma resulted. In the upper portions of these muscles earlier degenerative changes, as detailed above, were found.

HYPERTROPHIC STAGE OF BILIARY OBSTRUCTIVE CIRRHOSIS.

Balduin Lucké, M.D.

The liver lesion was clinically diagnosed as Hanot's cirrhosis. By this is understood a hepatic enlargement due to an inflammatory overgrowth of connective tissue between the individual or groups of liver cells. This is usually accompanied by more or less profound icterus but rarely by ascites. On section the greatly enlarged organ (which may weigh 5000 gm. or more) is found to be firm, usually of green color, with a but slightly granular surface and a somewhat uneven cut surface; the lobular marking is almost entirely lost. Hanot's cirrhosis is very rare in this country, but seems to occur more or less frequently in France. A condition simulating it is sometimes encountered in domestic and wild animals.

Case Report. J. K., aged twenty-five years, white male, born in Galicia, suffered with recurrent attacks of icterus. The first symptom (in 1915) was jaundice, a few months later he developed pain in the right shoulder. His gall-bladder was surgically drained

(1919), but no history of gall-stones can be obtained from the notes. At the time of operation the liver was indurated, extended to the umbilicus and had a somewhat rough edge. The spleen was palpably enlarged. A small section of the liver was removed, the histological diagnosis is said to have been Hanot's cirrhosis (this statement could not be confirmed since the tissue was lost). The patient was finally admitted to the Philadelphia Hospital (1920). He suffered from a deep icterus; the liver was enlarged to the umbilicus, the spleen extended four inches below the costal margin. Moderate ascites existed. Laboratory examinations disclosed a moderate secondary anemia, a normal white count and a negative Wassermann reaction. The temperature occasionally rose to 99°, the pulse varied from 80 to 100. On postmortem examination the skin was uniformly greenish-yellow, 800 cc of bile-tinged fluid were present in the abdominal cavity, and 150 cc of similar fluid in the pericardial sac. Liver weighed 3000 gm., measured 32 by 33 by 9 cm., and had a deep green color. The margin was slightly rounded. Surface was rather smooth, but showed occasional irregularly distributed hobnail elevations. Over the anterior surface and the lower margins just to the right of the gall-bladder numerous fibrous tags and a small scar at the margin were found. The diaphragm was generally adherent. The organ cut with greatly increased resistance; the cut surface was deep green. A very distinct, grayish-white fibrous tissue surrounded the individual lobules, only occasionally the fibrosis seemed to be multilobular. This interlobular fibrosis was uniformly distributed throughout the entire deep green organ. The gall-bladder was small, covered with fibrous adhesions; its wall was much thickened. The organ contained a small quantity of thin cloudy fluid. Lying free in the gall-bladder and extending into the cystic duct was a piece of a rubber catheter 4 cm. in length. After extraction of the tube the bile ducts proved to be patulous to probing. The spleen weighed 1630 gm., measured 26 by 15 by 3 cm., was firm, had a thickened capsule with many fibrous adhesions. On the dark red cut surface the fibrous framework stood out with some prominence, but the pulp was quite soft.

Microscopic examination of the liver shows a very pronounced monolobular fibrosis. The enormously thickened connective tissue is very dense and mainly perilobular. Only occasionally a small quantity of interlobular connective tissue is encountered. The bile ducts are greatly increased in numbers, of small size, and possess small lining cells. The hepatic cells are generally atrophic, and filled with dust-like bile pigment. Plugs and cylinders of inspissated bile are everywhere present. The spleen is markedly congested and moderately fibrotic.

The condition summarized here does not resemble Hanot's cirrhosis, but falls in the group of early (hypertrophic) biliary obstructive cirrhosis. It is not clear whether the original cause for the

obstruction was a stone, perhaps associated with a cholecystitis, or a choledochitis, but it seems that the retained catheter within the gall-bladder at least aided in further obstructing bile outflow.

HYDRONEPHROSIS, CONTAINING 4000 C.C. OF AMBER FLUID.

WALTER J. FREEMAN, M.D.

(From the Laboratory of Postmortem Pathology, Philadelphia General Hospital.)

Sudden and complete blocking of the ureter has been shown experimentally to produce cessation of the secreting function of the kidney with subsequent atrophy of the organ. Partial or intermittent obstruction to the outflow of urine brings about a dilatation of the ureter, the pelvis and later the calices of the kidney. If the condition goes far enough there is pressure atrophy of the whole kidney substance and the hydronephrosis becomes a mere sac of fluid in whose walls may be seen a few remnants of kidney tissue. There seems to be no limit to the size to which these sacs may grow, and when large they may cause confusion in diagnosis, being mistaken for ovarian cysts, retroperitoneal cysts or even ascites. In Keen's *Surgery* there is noted a hydronephrosis containing 86,000 cc of fluid, and Gould and Pyle mention a case of hydronephrosis weighing 100 pounds.

The specimen presented was removed from a white woman, aged forty-six years, who had been demented for two years before admission, and upon whom no history was obtained. Examination showed an obese woman, rather dyspneic, with an enlarged heart and a distended abdomen. In the right side of the abdomen was a large cystic mass, freely movable, which the patient was accustomed to push from one side to the other with a demented sort of enjoyment. Large amounts of urine (specific gravity 1016), containing no albumin and no casts, were frequently voided. The patient vomited once after admission, but there were no other gastro-intestinal symptoms. The heart-rate was very irregular and persistently over 140. The patient died three days after admission.

At necropsy there was found "a large retroperitoneal mass occupying the right side of the abdomen from the liver to the pelvis. The ascending colon rides on top of the mass and is almost black in color, but is probably not gangrenous. The mass itself fluctuates and is nowhere hard or nodular. The diaphragm on that side reaches the third interspace." The cystic mass proved to be a hydronephrosis containing 4000 cc of cloudy, dark amber fluid. No chemical examination was made.

The mass corresponds somewhat in shape to the normal kidney. There is definite lobulation evident which may be the evidences of renal lobulation, or more probably the contours of the hugely distended calices. The sac wall itself greatly resembles parchment paper and only at one area, for a diameter of 6 cm., can any suggestion of kidney tissue be observed. The ureter is dilated to the size of the small intestine as far down as the brim of the pelvis, where there is a dark, jagged calculus about 13 mm. long and 4 mm. in diameter, embedded in a mass of inflammatory tissue, apparently completely occluding the lumen.

Microscopic examination of the blackened ascending colon has revealed the following conditions: "The mucosa is uniformly necrotic. All coats are congested, edematous and infiltrated with polymorphonuclears. In one large vessel in the section there is a recent thrombus and about it the tissues are in a state of necrosis."

The heart was hypertrophied and dilated; the other kidney showed marked arteriosclerosis and multiple anemic infarcts.

The specimen is the largest hydronephrosis in the collection of the Philadelphia General Hospital. Aside from its size it is remarkable on account of the complicating colonic condition. The large size and free mobility of the sac caused it to elevate the ascending mesocolon until it interfered with the blood supply and caused a beginning gangrene.

BICORNATE UTERUS.

A. G. KERSHNER, M.D.

Patient was a white female, aged forty years, admitted to the Philadelphia General Hospital with cardiac decompensation, from which she died. She was one of a family of ten and had herself had three normal children and one miscarriage. In 1911, she had an operation for prolapse of the uterus and a left oöphorectomy. From then on her menses became less frequent and ceased at the age of thirty-five.

Autopsy disclosed a bicornate uterus, which evidently had nothing to do with her last illness, but is of interest because of her previous history of having three normal children.

PARTIAL TRANSPOSITION OF ABDOMINAL VISCERA.

A. G. KERSHNER, M.D.

Autopsy 6233, Philadelphia General Hospital, September 17, 1921. The specimen was obtained from a negro, male, aged fifty-seven

years. Clinical diagnosis: chronic myocarditis. On admission, he complained of dyspnea on exertion, epigastric distress and constipation for three years.

Physical Examination. Coarse rales throughout the chest, soft thrill in the midprecordium, presystolic and systolic murmurs in the mitral area and moderate arrhythmia. Blood-pressure, 150–84. Abdomen: lower border of the liver at the umbilicus. Edema of the extremities. Urine showed a heavy cloud of albumin with hyaline and granular casts.

Autopsy showed thoracic viscera in normal position; 700 cc of blood fluid were found in the pleural cavity. Both lungs were intensely congested and the left lung showed general hemorrhagic infarcts. The heart was greatly hypertrophied. All the abdominal viscera showed passive congestion. The stomach was on the right side and several splenic nodules were under the right diaphragm, while the inferior vena cava was on the left side of the abdominal aorta. The rest of the viscera were in normal *situ*.

TROPICAL INGUINAL GRANULOMA IN THE EASTERN UNITED STATES.

Alexander Randall, M.D.

We wish in a preliminary report to briefly call your attention to a condition supposedly occurring only in the tropics and its endemic existence in the temperate parts of the eastern United States.

Under the following variety of names—tropical inguinal granuloma, tropical ulcer, venereal granuloma, granuloma inguinale and granuloma pudendi—there has long been recognized by physicians practicing in the tropics and South America a disease which was supposedly limited to these countries.

Recently Symmers and Frost reported from the laboratories of the Bellevue Hospital, New York, 2 cases of tropical inguinal granuloma found in negroes of that city, and this number has recently been augmented in a later report by Campbell of 3 further cases found in the urological wards of that institution.

Recognizing the similarity of the lesions, as illustrated by Symmers and Frost, to certain cases that have been repeatedly seen on the urological service of the Philadelphia General Hospital, on commencing the service, January 1, I instituted a round-up, with the result that 5 men and 2 women were found in the institution suffering from this condition. These numbers have been increased since that time by 4 men and 1 woman patient, making a total of 12 cases under observation. Four further cases have been reported to us; 1 an inmate of the Penitentiary, who had on two previous

occasions been treated for this condition at the Philadelphia General Hospital; a second and a third observed by Dr. A. H. Lippincott, of Camden, N. J., after being diagnosed by our laboratory; and a fourth, a native of New Jersey, who is awaiting hospital admission, having been referred by Dr. J. L. Herman: a total of 16 cases.

The first and most important fact, when making such a diagnosis of a supposedly tropical disease as present in the temperate zone, is the unquestioned accuracy of the diagnosis. We have turned to the work of Aragao and Vianna, of Rio Janeiro, who are probably the world's authorities on this condition and the originators of the specific antimony treatment, and we have been able to corroborate and substantiate in our cases all the bacteriological data that they report, while the result of the specific treatment and the similarity of the appearance of the lesions, as we have seen them, to the splendid photographic and colored illustrations in their work have alone been almost self-substantiating.

This disease has been present, practically consistently, in the Philadelphia General Hospital as long as any of the attending physicians and nurses can remember. It has masqueraded here, as elsewhere, under various other diagnoses, among which may be mentioned lues, now ruled out, as in fact it has always been, by the repeatedly negative blood tests, lack of specific history and absolutely negative results with arsenic therapy; as chancroidal infection, to which it rarely bears any similarity, as destructive ulceration is particularly not a characteristic; as tuberculosis, though never substantiated by microscopic study; as condylomata, to which when seen in the female or about the anal region it bears a close similarity; and as carcinoma, to which the microscopic picture in 2 of our cases was almost identical.

Symptoms. The usual history is that the lesion started as a small papule, non-inflammatory, which, after rupture and the exudation of a slightly purulent fluid, refused to heal and exhibited progressive tendencies toward slow proliferation and spreading. The lesion in its purity (especially seen when involving the inguinal region) is a flesh-red exuberant overgrowth of soft granulation tissue. It has absolutely no similarity to an ulcer with its eroding, undermining, necrotic base. The center of the granuloma appears slightly depressed, and there is certainly a destructive action present, but the edges are redundant and overlap the apparently healthy skin margin. Exudate is scant, mucoid in character, of a non-offensive odor, and when wiped with gauze is easily removed, leaving a clean, blood-red surface similar in every respect to a large area of healthy granulation tissue, as seen in clean surgical wounds. This picture varies according to duration, size and location. The older lesions show at times tendencies toward cicatrization at some points while spreading in others, but this only occurs when flat non-chafing surfaces are involved. Large lesions, especially those in the perineum,

become bulbous, simulating condylomata acuminata, with large, rounded heads of new growth, the heads ofttimes with pearly-white surfaces of epithelization and deep crypts with raw, granulomatous surfaces. Secondary infection here causes the clean, odorless character to change.

As indicated by the name, the most frequent location is in the groin, spreading upward as far as the anterior-superior spine and downward through the fold of the groin, frequently involving the perineum, and in some cases following the fold of the nates and spreading to the buttocks. Prepucial lesions are likewise frequently associated and at times primary, and involvement here has given us the most destructive picture with a gradual erosion of the glans and even the shaft of the organ. In the female the labia majora share the brunt of the attack with the perineum and groin involvement in some cases. We have had 1 case, a male, with the granuloma limited to a proliferative growth about the anus.

The patients have few subjective symptoms. They suffer no pain or discomfort unless the involved areas are so placed as to cause chafing. The granuloma is practically painless to the touch and only deep pinching-up of the mass will cause suffering. Practically all of our patients have shown a definite degree of secondary anemia, but there has been a complete absence of pyrexia, chill, leukocytosis, throbbing, lassitude, or the usual concomitants of infectious processes.

Race. All of our cases, with one exception, have occurred in the negro. The one exception is that of a white male, in whom the lesion has likewise been atypical, simulating a phagedenic chancroidal sore with ragged, ulcerated edges. His bacteriological examination was positive and he may be harboring a double infection. He, however, has not responded to treatment with antimony.

Diagnosis. We have based our clinical diagnosis entirely upon the bacteriological finding of the specific organism. This is done by making smears from the exuding surface, in which will be found numerous large mononuclear plasma cells, whose protoplasm, on proper staining, will be found studded with the characteristic encapsulated diplobacillus. The therapeutic result from the use of antimony intravenously may likewise be taken as indicative of the accuracy of the diagnosis, for after three or four administrations the organism disappears entirely from the surface and cannot be found in smears.

Treatment. As pointed out by all previous writers, and substantiated by the histories of cases in the Philadelphia General Hospital, in years gone by the treatment of these lesions has been most disappointing until the present, when antimony was first instituted.

Local applications of salves, escharotics and antiseptics do no good whatsoever; vaccine therapy has been consistently a failure; excision is followed almost uniformly by recurrence before healing;

arsenic is of no benefit, and the roentgen ray alone has not given us any curative results, causing a slow cicatrization; but because of the dangers associated with its use, it has been possible to apply it only once every three weeks, and therefore requiring on an average from twelve to eighteen months to establish healing. Even with the roentgen ray the hospital experience in the years past has been disappointing, and probably at least 50 per cent of the cases returned with recurrences. Some of our present cases have had two or more admissions in passing years for return of their lesions after apparent complete healing under the roentgen-ray therapy, while several have been so long inmates of the institution that they have been put on the hospital's pay-roll and work as laborers about the buildings.

Following Vianna's work, we started giving antimony intravenously in the form of tartar emetic. The initial dose of 0.04 gm. was used, and this quickly advanced to a maximum dosage of 0.1 gm. Our first treatments were given daily, and most patients tolerated this until about ten doses had been given, but nearly all after that amount showed some symptoms of intolerance for the drug and we began intermitting the daily dosage, governing the time by symptomatic data. This intolerance consisted of rheumatoid pains in the joints associated with stiffness, especially seen in the early morning on rising, and most frequently located through the shoulder girdle, and as a general rule wore off during the course of the day. There have not been in any case symptoms of an alarming character.

The drug has been prepared by dissolving 0.1 gm. in 10 cc of saline solution, and is best put up and preserved by sealing under sterile precautions in that size glass ampoules. Intravenous administration is essential.

The lesion becomes bacteriologically sterile after the second or third dose of tartar emetic. Healing commences within forty-eight hours after the first administration and from then on almost daily progress can be appreciated. Epithelial proliferation starts at the edges and rapidly spreads inward, while often isolated islets of epithelium in the midst of the granuloma, before not seen or buried, start proliferation in the midst of the lesion and hurry the complete healing.

The phenomena of healing can best be pictured by comparing it to the use of arsphenamine in somewhat similar long-standing and untreated luetic skin lesions.

In some cases the administration of the drug causes a tingling, pricking sensation in the granuloma, immediately after the injection, and ofttimes an excess of mucoid secretion occurs for the first few days. Scabbing over of the surface takes place wherever the raw surfaces are in apposition, and thin crusts form around the periphery of open areas.

Results. Of our 12 personally observed cases, 8 are healed. As this is but a preliminary report, we will omit history *résumé.* Following the advice of Vianna we have persisted in giving all patients a course of injection after complete healing has been accomplished, to prevent the possibility of recurrence.

BACTERIOLOGY OF TROPICAL INGUINAL GRANULOMA.

JAMES C. SMALL, M.D.

(From the Laboratory of Bacteriology, Philadelphia General Hospital.)

Direct Smears. Direct smears from the lesions, properly prepared and stained, constitute a very reliable method of diagnosis. The material may be collected on sterile cotton applicators for either the smears or the cultures. Thin spreads of this material are essential. These are dried quickly in air and stained either by Wright's or Giemsa's stain. Wright's method is the more rapid and has given satisfactory results. The most difficult part of the procedure is to obtain the proper differentiation of the stained smear in distilled water. Even with the most intense Wright's staining this differentiation should not be carried on for more than fifteen to twenty seconds. Application of the water for too long entirely decolorizes the capsules of the organisms; for too short a period the capsules appear blue and the morphology of the bodies of the organisms cannot be observed clearly. With the best staining results the organisms appear as small rounded pink bodies with a dark blue coccoid body in the center, or more frequently as oval pink bodies with a bacillary or diplococcoid body occupying the longitudinal axis. The pink outer zone is a wide bacillary capsule; the dark blue central bodies represent metachromatic granules within the bacillary body proper. The true outline of the bacillary body can be seen only after the capsule has been entirely decolorized by differentiating with distilled water. In stained smears from the lesions some areas show organisms with capsules stained pale blue and obscurely differentiated central bodies; other areas show well-defined dark blue metachromatic granules surrounded by a pink capsule, which later, however, obscures the outline of the bacillus proper; and still other areas are seen in which the capsules have been entirely unstained and where the organisms appear as short, thick bacilli with rounded blunt ends occupied by the dark blue metachromatic granules. The organisms thus present a true bipolar-stained appearance with the intervening body shaft of the bacillus stained a pale blue. Always a few bacilli, shorter than those just described, stain solidly a deep blue.

The organisms are found within the cytoplasm of large mononuclear cells. In such they have well-defined capsules or may appear as nests of bacteria occupying a rounded area within the cell and revealing no capsules. In such nests the bipolar staining may be observed. The polymorphonuclear leukocytes do not contain the encapsulated forms. Encapsulated forms may appear free or in relation to cellular detritus. In the latter instances they occur chiefly in groups and in the neighborhood of large numbers of mononuclears. These presumably represent organisms released from the disintegrated cytoplasm of mononuclear cells. In the former instances they may occur singly and in no relation to cellular detritus.

Smears from the lesions are remarkably sparse in bacteria as compared with smear preparations from other types of ulcerative lesions about the genitalia. Staphylococci, streptococci, diphtheroid bacilli and bacilli having the morphology and staining character of the colon group have been observed widely scattered or in small clumps within the polymorphonuclear cells.

Cultures. The granuloma organisms have been grown in cultures in four instances. Of the various media and methods tried, surface inoculation of Sabouraud's maltose agar (2 per cent acid), as recommended by Barao and Vianna, proved the most useful. This degree of acidity tends to inhibit some of the contaminating bacteria and permits profuse growth of the granuloma bacillus. The growth is quite characteristic after twenty-four hours' incubation. Colonies appear slightly gray-white, moist, glistening, dome-shaped on round regular bases from 1 to 3 mm. in diameter. When touched with an inoculating wire they appear quite viscid, and have the consistency and appearance of thin starch paste. By transmitted light they are translucent and have a slightly brownish tinge. They are usually the largest colony appearing in these mixed cultures of the material taken directly from the lesions and are very readily recognized.

In subcultures growth occurs on all of the simpler media. Enriched media is not necessary. On semisolid media the character of the growth does not differ essentially from that described above. In fluid media there is diffuse turbidity with a surface ring tending to adhere to the sides of the culture tube and to climb slightly above the level of the liquid. Later sedimentation occurs. Growth is profuse even in 1 per cent peptone water. In litmus milk there is acid production and coagulation within twenty-four hours. On potato growth it is profuse, moist and slightly brownish in color. There is a decided blackening of the potato.

Smears from cultures, when stained with Wright's stain, show essentially the morphological details previously described; in smears from Sabouraud's media and from moist glucose or plain agar, wide capsules are readily demonstrated, so that the organisms appear

as do the encapsulated ones in direct smears from the lesions. In smears from broth cultures capsules are not demonstrated, so that the organisms from twenty-four-hour-old cultures appear as short, plump bacilli exhibiting irregular staining, and for the most part showing a dark area at either pole with pale blue intervening. In older cultures, especially in media containing a carbohydrate which has been fermented with decided acid production, long forms occur. These forms also stain irregularly, presenting dark blue banded areas, alternating with pale blue areas throughout the length of the organism.

Our study of the organism may be tabulated briefly: Non-motile, non-sporulating, encapsulated bacillus; Gram-negative, showing metachromatic granules as well as capsules with Romanowski staining; it does not liquefy gelatin or coagulated serum; it hemolizes blood in agar plates; it does not form indol; coagulates and acidifies milk within twenty-four hours. It ferments dextrose, levulose, lactose, galactose, saccharose, maltose, arabinose, mannitol, salicin, inulin and dextrin. It does not ferment dulcitol and rice starch.

Pathogenicity. Intraperitoneal inoculation kills white mice and guinea-pigs in twenty-four to forty-eight hours. The organisms are recovered at autopsy from the peritoneal fluid, the blood and the various internal organs.

Cutaneous inoculation of white mice, guinea-pigs, rabbits, cats and dogs all failed to produce definite lesions.

Intradermal inoculation of dogs was also negative.

Subcutaneous inoculation of white mice and guinea-pigs produced an inflammatory reaction, going on to abscess formation in some instances but always with spontaneous and rapid healing. In dogs and cats no abscess formation occurred, only a slight inflammatory reaction being noted.

In rabbits it produced large subcutaneous infiltrations with abscess formation and spontaneous rupture producing ulcers, some of which have failed to heal after an observation period of six weeks.

CARRIERS OF HEMOLYTIC STREPTOCOCCI.

James C. Small, M.D.

On the basis of findings in throat cultures, the incidence of hemolytic streptococci was studied in normal individuals and in patients with measles.

I. The normal individuals are classified into three groups:

1. Those resident in the hospital, including doctors, nurses and ward personnel.

2. Those resident in military camps.

3. Those resident in outlying country districts.

(a) Among attendants in hospital wards the incidence of H. S. was highest during the period when H. S. infections were most prevalent among patients in the wards. No symptoms were caused by the appearance of H. S. in the throats of normals.

(b) Among men on duty in camps a 21.9 per cent incidence in 274 men studied at Camp Funston and a 7.4 per cent incidence in 337 men studied at Camp Pike.

(c) Among men from outlying country districts the incidence of H. S. in throats was low; 64 men were studied without a single positive throat culture for H. S. When sputum was inoculated into mice from 50 of these men, 3 of them showed a few colonies of H. S. on cultures from peritoneal exudate from mice.

II. The patients under treatment in measles wards showed:

1. An incidence of H. S. on admission lower than that found in normal men in companies from which the measles cases came.

2. An increasing incidence of H. S. with duration of stay in the hospital.

3. An increasing incidence of H. S. with duration of the camp epidemic of measles.

Cultures were made from the throats of these patients on admission to the hospital, and patients showing positive for H. S. were treated in wards separate from those not showing these organisms in throat cultures. All patients were followed up at weekly intervals during the period of hospitalization. Streptococcus positive cases were removed to separate wards on identification in these weekly surveys.

Among 787 patients with measles, 37 were found to have throat cultures positive for H. S. on admission and 205 additional cases acquired H. S. while under hospital treatment.

III. Three classes of H. S. carrier are defined:

1. The chronic carrier, represented by individuals harboring small numbers of H. S., usually in ragged hypertrophied tonsils, over long periods of time.

2. The acute carrier, represented by those individuals who have active symptoms following the appearance of H. S. in their throats. The evidence presented shows that the H. S. tend to disappear from the throats of these patients with the passing of the acute clinical conditions. The indications are that the H. S. carried by such individuals have a higher virulence than those carried by the chronic carriers.

3. The contact carrier, represented by individuals who acquire H. S. under conditions where H. S. is passing freely from person to person but who do not present any clinical signs indicating the presence of these organisms. These contact carrier states are of short duration, in many cases less than two weeks.

IV. Relation of different types of carrier to the serious streptococcic complications of respiratory diseases.

1. The chronic carrier maintains the manifestations of H. S. The chronic endemic carrier serves as a primary force for development of contact carriers.

2. The contact carrier serves to pass the H. S. to others, so that large numbers of these carriers develop under conditions where individuals are crowded together. The passing of a strain of H. S. through a series of contact carriers, while causing no symptoms in these individuals, presumably tends to raise the virulence of the strain passed to a point where it begins to produce symptoms in those acquiring it, when acute carriers develop.

3. The development of acute carriers calls attention to the epidemic prevalence of H. S. at a time when it is too late to institute effective prophylactic measures.

The evidence at hand indicates that serious streptococcic complications in respiratory diseases follow closely the appearance of H. S. in the throat, *i. e.*, in most cases within one week.

BRONCHIECTASIS.

Hugh M. Miller, M.D.

(From the Laboratories of the Philadelphia General Hospital.)

A man, aged forty-three years, was admitted to the medical wards of the Philadelphia General Hospital because of loss of strength and of 30 pounds of weight in the past year. Gastric symptoms predominated, any lung symptoms being completely overshadowed. It was noted that the patient was incontinent of urine and had difficulty in starting a stream, with suprapubic pain.

On examination, his appearance was anemic and emaciated. Scaphoid abdomen, with enlarged veins over the lower abdomen and large inguinal glands. There was an increased resistance and tenderness in the epigastrium.

Rectal examination negative. Laboratory examination—Blood count: Hemoglobin, 75 per cent; red blood cells, 4,660,000; white blood cells, 13,700; polymorphonuclear leukocytes, 60 per cent; lymphocytes, 38 per cent; transitionals, 2 per cent. Urine: Sp. gr., 1010; trace of albumin; occasional granular cast.

Blood Wassermann, negative.

Gastric analysis: Free hydrochloric acid, 0; total acidity, 10; no lactic acid or occult blood.

After five months in the hospital he died, with a clinical diagnosis of carcinoma of the stomach.

At autopsy there was found to be chronic ulcerative tuberculosis of the middle lobe of the right lung with several cavitations, repre-

senting a dilated and ulcerated bronchus. At the apex of the right upper lobe is a cheesy nodule, 3 mm. in diameter, over which the pleura is slightly thickened and retracted.

The kidneys show cortical and medullary tuberculosis, and the stomach chronic catarrh.

The toxemia was due to the tuberculous nephritis and ulcerative tuberculous bronchiectasis. The gastric symptoms resulted in the lung and kidney symptoms being overlooked.

LUNG ABSCESS SECONDARY TO SUBDIAPHRAGMATIC ABSCESS.

HUGH M. MILLER, M.D.

(From the Laboratories of the Philadelphia General Hospital.)

Abscess of the lung resulting from direct extension of an abscess in the peritoneal cavity is not common. This was a case of perforation of the diaphragm with subdiaphragmatic abscess, associated with ulceration of a primary carcinoma of the splenic flexure of the colon.

The history states that a white man, aged seventy-five years, has had severe pain in the left side for three months, during which time he had lost 75 pounds in weight. Constant cough and hiccoughs were noted. He died in the men's tuberculosis ward of the Philadelphia General Hospital, with the clinical diagnosis of pulmonary tuberculosis.

At autopsy the left lower lobe of the lung is consolidated about an irregular necrotic abscess in the lower portion and no tuberculosis is found.

MEGACOLON.

HUGH M. MILLER, M.D.

(From the Laboratories of the Philadelphia General Hospital.)

A middle-aged negro male, presenting definite evidence of a toxic confusional psychosis, with alcoholism as a basic factor, depressed, hallucinated, delusional. There is no history of intestinal disturbance as far as diarrhea or constipation is concerned; distention of abdomen first noted six years after admission, but noted several times later, usually in conjunction with swelling of the lower extremities. Death occurred suddenly. Diagnosis: Intestinal obstruction, toxic psychosis, alcoholic.

Autopsy (kindness of Dr. Wadsworth). On opening the abdomen a hugely distended colon bulged through the incision; this mass was found to be chiefly descending colon and sigmoid. However, the colon was somewhat enlarged as far as the ileocecal valve. Ten cm. from the anus the rectal plications are 1 cm. in thickness, dense and firm. Serosa is smooth and glistening, sigmoidal portion of the mucosa is smooth and somewhat edematous, and the whole wall of the gut thickened. Circumference, 30 cm. The sigmoid forms a saccular dilatation 30 cm. along the lesser curvature or mesenteric attachment and 60 cm. along the greater curvature. The descending colon measures 20 cm. in circumference. No obstruction was found in either the colon, rectum or sphincter. The pericardium showed extensive black, dotted pigmentation; though not cicatricial in appearance, these dots look as if they had been remnants of previous acute pericarditis. The lungs were pushed well up, the left occupying only about one-third of its usual space and adherent by bands, which may have existed for years. The left lung is collapsed.

INCIDENTAL CARCINOMA OF THE THYROID WITH METASTASIS TO THE KIDNEY.

Edward T. Crossan, M.D.

(From the Laboratory of Postmortem Pathology, Philadelphia General Hospital.)

The specimen in this case is a slide showing adenocarcinoma of the thyroid which was obtained from autopsy 5637, performed at the Philadelphia General Hospital on December 21, 1920.

The subject, F. G., was admitted to the hospital on October 17, 1920, and died on October 20. The clinical diagnosis was bronchopneumonia and cardiorenal degeneration. The symptoms, the physical examination and the laboratory findings pointed to the latter diagnosis. There were no notes about the thyroid. At the autopsy the clinical diagnosis was confirmed.

In making the external examination at the autopsy table Dr. Crawford noted an enlargement of the thyroid. On exposing the mass it was found to be the thyroid gland which was enlarged throughout and of irregular shape. The left lobe cut with increased resistance and the cut surface showed calcified deposits, cystic areas and a loss of connective tissue. The microscopic picture (Drs. A. J. Smith and W. P. Belk) was that of a cystic and fibrous goiter, with some areas of calcification from which there had sprung an adenocarcinoma.

Added interest is given to the case from the fact that there was metastasis to both kidneys and also a pseudomyxoma peritonei in the appendicular region.

UNUSUAL HYPERTROPHY OF A CHILD'S HEART.

Edward T. Crossan, M.D.

The chief point of interest in this specimen is the intense hypertrophy of the heart. The organ (from autopsy 5727, Philadelphia General Hospital) is that of a colored boy, aged fourteen years. It weighs 820 gm., which is three and one-half to four times the normal weight of the heart at this age. This specimen, therefore, compares very favorably with the classical case reported by Stokes. The walls of all of the cavities of the heart are hypertrophied, but the hypertrophy is most marked in the left ventricle. Dr. Crawford, who performed the autopsy, noted that all of the papillary muscles were markedly hypertrophied. In this heart there are also present a chronic ulcerative and an acute ulcerative endocarditis of the mitral and the aortic leaflets, a chronic ulcerative mural endocarditis of the left ventricle, a chronic interstitial myocarditis and arteriosclerosis.

One factor, which played a large part in producing this unusual hypertrophy, was the chronic adhesive and obliterative pericarditis present. At the autopsy it was found that the two layers of the pericardium were continuous throughout. Other associated lesions were bronchopneumonia, acute fibrinous pleuritis and acute splenitis.

A review of the clinical history shows that the boy was admitted to the service of Dr. Riesman at the Philadelphia General Hospital on July 3, 1920, with a diagnosis of subacute endocarditis. There was a family history of heart trouble for three generations. Three days before admission the boy was seized with shortness of breath, which was preceded by an attack of rheumatism lasting three or four weeks. On physical examination, there were found hypertrophied tonsils with pus in the crypts, an overacting heart, a loud mitral systolic murmur and a heart enlarged 2.5 cm. to the right of the sternum.

Six days after admission loud systolic and diastolic aortic murmurs were heard; from this date until August 4 the progress was uneventful. On the latter date the patient developed tonsillitis, and on October 2 a tonsillectomy was done. The patient's condition grew gradually worse, and on December 18 a positive blood culture was obtained, showing Streptococcus viridans, and death intervened eight days later. During the illness the temperature ranged from normal to 103°. Blood examination showed red blood cells, 3,140,000; white blood cells, 25,000; hemoglobin, 50.

RETICULOSIS.

Edward B. Krumbhaar, M.D.

(From the Laboratory of Clinical Pathology, Philadelphia General Hospital.)

1. Erythrocytes revealing a more or less extensive reticulum (granulofilamentous substance) by the methods of vital staining may be conveniently designated "reticulocytes."

2. The reticulum is of protoplasmic origin and indicates an intermediate stage between the erythroblast and the adult erythrocyte. A simple method for the recognition and estimation of these cells is described.

3. The great delicacy of the tests for these cells and the greater constancy and delicacy of their variations in the peripheral blood make them a more valuable criterion of the functional activity of the bone-marrow than the study of polychromatophilia or nucleated forms.

4. In the blood of dogs made plethoric by repeated transfusions of blood, the reticulocytes diminished or disappeared entirely during the plethoric stage. With the occurrence of a hemolytic anemia a reticulosis occurred which in one instance reached 81 per cent.

5. The average percentage of reticulocytes in normal adult man I have found to be 0.3 per cent, with a range from 0.1 to 1 per cent.

6. A graph of the reticulocyte count in infants is given showing that it rapidly falls in the first twenty-four hours from 5 to 1.8 per cent and has reached an approximately normal level (less than 1 per cent) by the end of the first week.

7. The range in laboratory animals was found to be more variable: Monkey, 0 to 1.8 per cent; cat, 0 to 1.4 per cent; dog, 0.1 to 1.4 per cent; rabbit, 0.6 to 1.8 per cent; mouse, 1 to 6 per cent.

A COMPARATIVE STUDY OF ENCAPSULATED BACILLI ISOLATED FROM CASES OF GRANULOMA INGUINALE.

Louis A. Julianelle and James C. Small, M.D.

(From the Laboratory of Bacteriology, Philadelphia General Hospital.)

The purpose of this investigation was to determine whether or not the encapsulated bacilli isolated from the lesions of granuloma inguinale bear any relation to the Bacillus mucosus capsulatus group of bacteria. A comparative study was made of three strains of encapsulated bacilli from cases of granuloma inguinale; eight strains of Friedländer bacillus of respiratory tract origin; two stock strains of Bacillus aërogenes; and one stock strain of bacillus of rhinoscleroma.

The study developed along three lines: (*a*) Morphological, (*b*) cultural and (*c*) serological. The serological work is in progress, and no report will be made of it at this time. An analysis of the data from the morphological and cultural studies will be presented.

The encapsulated bacilli of granuloma origin in common with the Bacillus mucosus capsulatus group show the following characters: They are non-motile, encapsulated, non-sporulent, aërobic bacilli. They stain readily by the aniline dyes and do not retain the gentian violet by Gram's method. They do not produce indol in peptone water and do not liquefy gelatin. They show a wide range of carbohydrates which they are able to ferment, usually with gas production, but are unable to attack dulcitol.

By using fifteen carbohydrates it was found that differential characters could be shown best with dextrose, lactose, sucrose, starch and dulcitol. The bacillus of rhinoscleroma differed from the others in its inability to produce gas in dextrose broth. The Bacillus aërogenes is differentiated by its fermenting dulcitol with gas production. The eight strains of Friedländer's bacillus and the three strains of encapsulated bacilli of granuloma origin are all capable of producing acid and gas in dextrose, but are incapable of fermenting dulcitol. These may be subdivided among themselves according to the fermentation reactions shown with lactose, sucrose and starch:

    1. Those fermenting lactose, sucrose and starch.

    2. Those fermenting lactose, but not sucrose and starch.

    3. Those fermenting neither lactose, sucrose nor starch.

Within the first group fall two of the granuloma strains and four of the respiratory strains; in the second group one granuloma strain and three of the respiratory strains; while only one of the respiratory strains falls into the third group.

No differentiation could be established by a study of the abilities of these organisms to utilize protein. They are all weakly proteolytic but incapable of attacking gelatin. In broth they do not produce indol nor creatinin. They all form ammonia and reduce nitrates to nitrites.

In so far as the present studies furnish data for analysis, the encapsulated bacilli isolated from the lesions of patients suffering from granuloma inguinale belong to the Bacillus mucosus capsulatus group.

CHEMISTRY OF THE BLOOD IN DISEASE.

William G. Karr, M.D.

(From the Biochemical Laboratory, Philadelphia General Hospital.)

A general discussion of present status of this subject.

CARCINOMA OF THE STOMACH WITH METASTASES TO BOTH ADRENALS.

EDWARD WEISS, M.D.

C. K., a white male adult, aged fifty years, was admitted to the Philadelphia General Hospital, August 21, 1920, complaining of pain in the abdomen. His family history and past medical history are unimportant. The pain began four weeks before admission, bears no relation to the taking of food and is not associated with vomiting. Patient states that his appetite is fair, his strength poor and that he has lost 20 pounds in weight in the past two weeks.

Physical examination showed an emaciated individual with a scaphoid abdomen. There was slight rigidity in the lower right quadrant of the abdomen, with pain on deep palpation. Blood count showed a secondary anemia; the blood-pressure on admission was 85 systolic and 40 diastolic; fluoroscopic examination of the abdomen demonstrated a carcinoma of the pyloric end of the stomach.

Necropsy showed a large cauliflower growth of the pyloric end of the stomach, and other than invasion of the perigastric lymph nodes there were no metastases except to the adrenal glands, both being involved to about the same degree. The histological diagnosis is medullary carcinoma of the stomach with metastases to both adrenals.

The striking clinical feature was the marked asthenia with low blood-pressure and slow pulse; the unusual pathological feature was the curious metastasis.

PRIMARY BRONCHIAL CARCINOMA.

WILLIAM P. BELK, M.D.

This growth occurred in a white male subject, aged fifty-six years, at the Philadelphia General Hospital (autopsy No. 6050 by Dr. Lucké). A diagnosis of sarcoma of the mediastinum was made clinically from the roentgen-ray report, signs of consolidation in the left upper lung, loss of voice, cough and repeated negative examination of the sputum for tubercle bacilli. There was also pain in the left chest and arm, and the left pupil was dilated. There was no anemia. Death from inanition.

At autopsy, the left lung was firmly adherent to the chest wall at all points. There was no pleural fluid. A fungoid mass projecting laterally had eroded the fourth and fifth ribs. The weight of the organ was 1645 gm. It was entirely consolidated, except the lower border posteriorly. The cut section showed a pale-gray,

coarsely nodular tumor in which were areas of hemorrhage and necrosis. Bronchioles were not visible. There were similar masses, smaller and apparently metastatic, in the mediastinal lymph nodes and in the right lung.

Histological sections showed large masses of epithelial cells supported on a delicate fibrous stroma. These cells were large, round, oval or polyhedral, had a definite cytoplasm and large, dark-staining centrally placed nuclei. Variations in size, shape and staining were marked. Mitotic figures were few. Necrosis and hemorrhage were marked. Other areas showed imperfectly formed glandular tubules, the cells of which were columnar or cubic, with nuclei at the bases. Some of these suggested goblet cells. There was, however, no noticeable formation of mucus. Bronchioles were not noted.

The origin of this tumor was either in the bronchial mucosa or the bronchial mucous glands, as the cells nowhere resembled the alveolar epithelium. The advanced state of the growth with marked tissue destruction made it impossible to decide between these two sites of origin.

HISTOPATHOLOGY OF TROPICAL INGUINAL GRANULOMA.

William P. Belk, M.D.

(From the Laboratory of Postmortem Pathology, Philadelphia General Hospital.)

The microscopic picture presents a very cellular area supported by a relatively small amount of young connective tissue. The cells are chiefly endothelial leukocytes with a varying number of polymorphonuclear leukocytes, the proportion depending upon the chronicity of the process; the more chronic the process the larger the proportion of endothelial cells. Small lymphocytes are also very numerous, and occasionally an eosinophil is seen. Formation of bloodvessels is seen as in any granulating tissue. There is a rather marked proliferation of the squamous epithelium of the skin, extending for some extent into the underlying tissues. In 1 case this was quite suggestive of squamous-cell carcinoma. The whole process is surrounded by dense hyaline connective tissue. The organism described by Small has not been stained successfully in tissue in this laboratory, the chief difficulty being to show the capsule. The bipolar bacillus, however, has been stained, and this apparently is found only in the endothelial cells.

TUBERCULOUS PERICARDITIS.

Baxter L. Crawford, M.D.

J. D., colored, male, aged forty-three years, was admitted to the Philadelphia General Hospital, October 25, 1920, suffering with cardiac symptoms, and died twenty-four hours later.

Clinical Diagnosis. Myocarditis with failing compensation—acromegaly.

At Autopsy. The pericardium was found to be markedly thickened, and adherent by fairly dense adhesions entirely obliterating the cavity. On separating the two layers, numerous small pin-head-sized, slightly raised, whitish foci could be seen on the surfaces of both layers of the pericardium.

The peribronchial and mediastinal lymph nodes were enlarged. Some the size of an English walnut, firm in consistency, on section show fibrosis and numerous small yellowish foci throughout the substance. A few of the mesenteric and postperitoneal lymph nodes were also enlarged and showed fibrosis and the presence of yellowish foci in the substance.

One interesting feature concerning the case was the distribution of the tuberculous process, namely, advanced tuberculous lymphadenitis and tuberculous pericarditis with practically no evidence of the infection in other organs. There were a few fibrosed and calcified lesions in both lungs.

Bacteriology. One of the foci from the surface of the pericardium was crushed and in the smears a few acid-fast bacilli were found.

Histological Report. Sections show the pericardium to be thickened with an organizing fibrinous exudate with many small focal areas of necrosis surrounded by mononuclear leukocytic infiltration in which are many giant cells. The myocardium shows no evidence of the inflammatory infiltration.

Diagnosis. Chronic tuberculous pericarditis; chronic fibrous tuberculous lymphadenitis.

Postmortem was performed at the pathological department of the Philadelphia General Hospital. I am indebted to Dr. Krumbhaar for the privilege of submitting this report.

ACROMEGALY WITH PITUITARY TUMOR—ACIDO-PHILIC ADENOMA OF ANTERIOR LOBE.

Edward B. Krumbhaar, M.D.

This brain is from a negro who was admitted to the Philadelphia General Hospital, October 25, 1920, with the diagnosis of acromegaly

and cardiac decompensation. The acromegaly was so obvious that the diagnosis was made by an onlooker as the patient arrived in a taxicab. Death occurred the next day from pulmonary edema, and on autopsy, this walnut-sized tumor of the hypophysis was found compressing the optic chiasm, and widening the sella turcica. The histological examination showed it to be comprised almost entirely of acidophilic cells resembling those normally found in the anterior lobe. The tumor was encapsulated and had the structure of an adenoma. The remains of the normal anterior lobe, infundibulum and posterior lobe were found flattened on its posterior surface.

The chief interest in this case to me was the comparison with an apparently similar pituitary adenoma of a case without acromegaly that I autopsied some twelve years ago at the Pennsylvania Hospital. Microscopically, however, this former adenoma was composed entirely of chromophobe cells. These 2 cases, therefore, support the theory that the actively functioning acidophilic cells (either hyperplastic in the anterior lobe, or in an adenoma) are necessary factors in the causation of acromegaly (or giantism, if occurring in youth). It is, of course, recognized that cases of acromegaly have been found without an increase of acidophilic pituitary cells. This does not necessarily negative the above theory, however, if one may presume that in such cases, acidophilic cells were present during the formative period of the acromegaly, but later vanished with the secondary changes that have been shown by Cushing and others frequently to occur in pituitary disease. (The two brains, microscopic slides and photographs accompanied the above demonstration.)